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NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	JAN 02	STN pricing information for 2008 now available
NEWS	3	JAN 16	CAS patent coverage enhanced to include exemplified prophetic substances
NEWS	4	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS	5	JAN 28	MARPAT searching enhanced
NEWS	6	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS	7	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment
NEWS	8	JAN 28	MEDLINE and LMEDLINE reloaded with enhancements
NEWS	9	FEB 08	STN Express, Version 8.3, now available
NEWS	10	FEB 20	PCI now available as a replacement to DPCI
NEWS	11	FEB 25	IFIREF reloaded with enhancements
NEWS	12	FEB 25	IMSPRODUCT reloaded with enhancements
NEWS	13	FEB 29	WPINDEX/WPIDS/WPIX enhanced with ECLA and current U.S. National Patent Classification
NEWS	14	MAR 31	IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats
NEWS	15	MAR 31	CAS REGISTRY enhanced with additional experimental spectra
NEWS	16	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
NEWS	17	MAR 31	LPCI now available as a replacement to LDPCI
NEWS	18	MAR 31	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS	19	APR 04	STN AnaVist, Version 1, to be discontinued
NEWS	20	APR 15	WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS	21	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS	22	APR 28	IMSRESEARCH reloaded with enhancements
NEWS	23	MAY 30	INPAFAMDB now available on STN for patent family searching
NEWS	24	MAY 30	DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
NEWS	25	JUN 06	EPFULL enhanced with 260,000 English abstracts
NEWS	26	JUN 06	KOREAPAT updated with 41,000 documents
NEWS	27	JUN 13	USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications
NEWS	28	JUN 19	CAS REGISTRY includes selected substances from web-based collections
NEWS	29	JUN 25	CA/CAplus and USPAT databases updated with IPC reclassification data

10/568,655

07/27/2008

NEWS 30 JUN 30 AEROSPACE enhanced with more than 1 million U.S.  
patent records  
NEWS 31 JUN 30 EMBASE, EMBAL, and LEMBASE updated with additional  
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organizations  
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Assistant and BLAST plug-in  
NEWS 33 JUN 30 STN AnaVist enhanced with database content from EPFULL

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AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 17:17:18 ON 27 JUL 2008

=> FILE REG

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 17:17:41 ON 27 JUL 2008

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STRUCTURE FILE UPDATES: 25 JUL 2008 HIGHEST RN 1036147-29-1

DICTIONARY FILE UPDATES: 25 JUL 2008 HIGHEST RN 1036147-29-1

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TSCA INFORMATION NOW CURRENT THROUGH January 9, 2008.

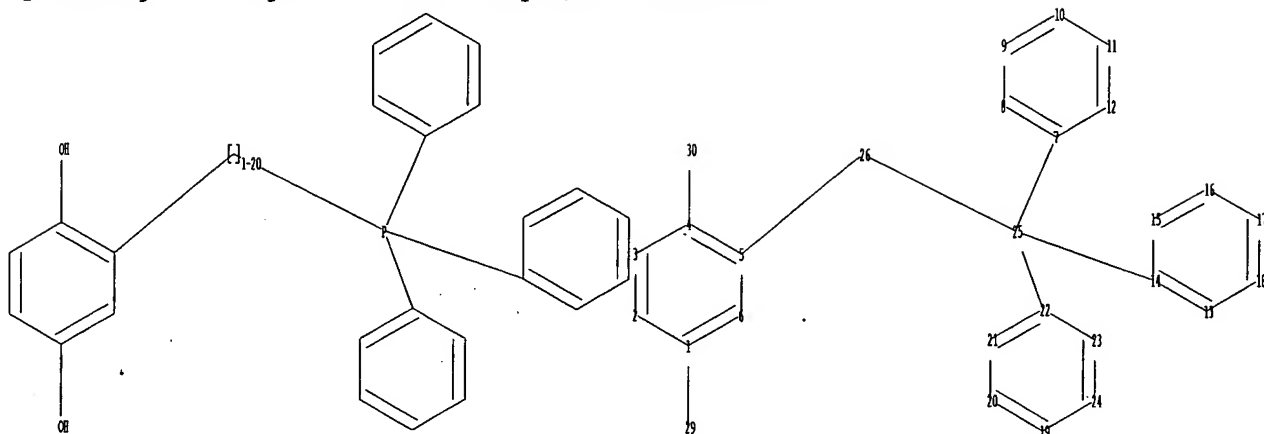
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=&gt;

Uploading C:\Program Files\Stnexp\Queries\GM102.str



chain nodes :

25 26 29 30

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23  
24

chain bonds :

1-29 4-30 5-26 7-25 14-25 22-25 25-26

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-18  
14-15 15-16 16-17 17-18 19-20 19-24 20-21 21-22 22-23 23-24

exact/norm bonds :

1-29 4-30

exact bonds :

5-26 7-25 14-25 22-25 25-26

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-18  
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Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom  
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom  
20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:CLASS 26:CLASS 29:CLASS 30:CLASS

L1 STRUCTURE UPLOADED

=&gt; S L1 FULL

FULL SEARCH INITIATED 17:18:17 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 532 TO ITERATE

100.0% PROCESSED 532 ITERATIONS

16 ANSWERS

SEARCH TIME: 00.00.01

L2 16 SEA SSS FUL L1

=&gt; FILE CAPLUS

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

178.36

178.57

FILE 'CAPLUS' ENTERED AT 17:18:31 ON 27 JUL 2008

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FILE COVERS 1907 - 27 Jul 2008 VOL 149 ISS 5

FILE LAST UPDATED: 25 Jul 2008 (20080725/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

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=&gt; S L2

L3 16 L2

=&gt; D L3 IBIB ABS HITSTR 1-16

L3 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:459952 CAPLUS

DOCUMENT NUMBER: 149:47117

TITLE: Rapid and extensive uptake and activation of hydrophobic triphenylphosphonium cations within cells  
AUTHOR(S): Ross, Meredith F.; Prime, Tracy A.; Abakumova, Irina; James, Andrew M.; Porteous, Carolyn M.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Wellcome Trust/MRC Building, Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 0XY, UK

SOURCE: Biochemical Journal (2008), 411(3), 633-645

CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mitochondria-targeted mols. comprising the lipophilic TPP (triphenylphosphonium) cation covalently linked to a hydrophobic bioactive moiety are used to modify and probe mitochondria in cells and in vivo.

However, it is unclear how hydrophobicity affects the rate and extent of their uptake into mitochondria within cells, making it difficult to interpret expts. because their intracellular concentration in different compartments is uncertain. To address this issue, we compared the uptake into both isolated mitochondria and mitochondria within cells of two hydrophobic TPP derivs., [3H]MitoQ (mitoquinone) and [3H]DecylTPP, with the more hydrophilic TPP cation [3H]TPMP (methyltriphenylphosphonium). Uptake of MitoQ by mitochondria and cells was described by the Nernst equation and was .apprx.5-fold greater than that for TPMP, as a result of its greater binding within the mitochondrial matrix. DecylTPP was also taken up extensively by cells, indicating that increased hydrophobicity enhanced uptake. Both MitoQ and DecylTPP were taken up very rapidly into cells, reaching a steady state within 15 min, compared with .apprx.8 h for TPMP. This far faster uptake was the result of the increased rate of passage of hydrophobic TPP mols. through the plasma membrane. Within cells MitoQ was predominantly located within mitochondria, where it was rapidly reduced to the ubiquinol form, consistent with its protective effects in cells and in vivo being due to the ubiquinol antioxidant. The strong influence of hydrophobicity on TPP cation uptake into mitochondria within cells facilitates the rational design of mitochondria-targeted compds. to report on and modify mitochondrial function in vivo.

IT 845959-55-9, Mitoquinol

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(IDTP localizes predominantly to mitochondria with human fibroblasts)

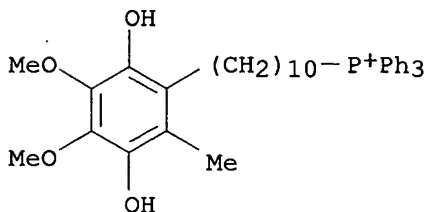
RN 845959-55-9 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

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CRN 747398-82-9

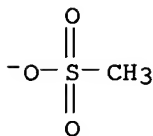
CMF C37 H46 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:965666 CAPLUS

DOCUMENT NUMBER: 148:135860

TITLE: Mitochondria-targeted antioxidants do not prevent tumor necrosis factor-induced necrosis of L929 cells

AUTHOR(S): Jarvis, Reagan M.; Goettert, Jana; Murphy, Michael P.; Ledgerwood, Elizabeth C.

CORPORATE SOURCE: Department of Biochemistry, University of Otago, Dunedin, N. Z.

SOURCE: Free Radical Research (2007), 41(9), 1041-1046

CODEN: FRARER; ISSN: 1071-5762

PUBLISHER: Informa Healthcare

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mitochondrial production of reactive oxygen species (ROS) is widely reported as a central effector during TNF-induced necrosis. The effect of a family of mitochondria-targeted antioxidants on TNF-induced necrosis of L929 cells was studied. While the commonly used lipid-soluble antioxidant BHA effectively protected cells from TNF-induced necrosis, the mitochondria-targeted antioxidants MitoQ3, MitoQ5, MitoQ10 and MitoPBN had no effect on TNF-induced necrosis. Since BHA also acts as an uncoupler of mitochondrial membrane potential, two addnl. uncouplers were tested. FCCP and CCCP both provided dose-dependent inhibition of TNF-induced necrosis. In conclusion, the generation of mitochondrial ROS may not be necessary for TNF-induced necrosis. Instead, these results suggest alternative mitochondrial functions, such as a respiration-dependent process, are critical for necrotic death.

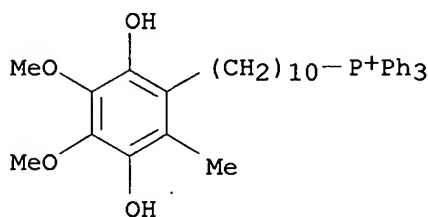
IT 299975-19-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitochondria-targeted antioxidants do not prevent tumor necrosis factor-induced necrosis of L929 cells)

RN 299975-19-2 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:763808 CAPLUS  
 DOCUMENT NUMBER: 147:134492  
 TITLE: Use of mitochondrially targeted antioxidant in treatment and prevention of drug-induced liver disease  
 INVENTOR(S): Buck, Charles; Denk, Helmut; Frohlich, Eleonore; Gutmann, Birgit; Hecht, Peter; Kvietikova, Ivica; Otte, Marcus; Schatz, Gottfried; Stumptner, Cornelia; Wightman, Lionel; Zatloukal, Kurt  
 PATENT ASSIGNEE(S): USA  
 SOURCE: U.S. Pat. Appl. Publ., 21pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070161609	A1	20070712	US 2006-328247	20060110
PRIORITY APPLN. INFO.:			US 2006-328247	20060110
OTHER SOURCE(S):	MARPAT 147:134492			

AB The present invention relates to the method of treatment or prophylaxis of patients with drug-induced liver diseases which comprises administering to the patient in need thereof a therapeutically effective amount of a mitochondrially targeted antioxidant compound e.g. derivs. of vitamin E, coenzyme Q10 or a glutathione peroxidase mimetic. The present invention also relates to pharmaceutical compns. containing the antioxidant(s) intended for such use.

IT 845959-55-9  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (use of mitochondrially targeted antioxidant in treatment and prevention of drug-induced liver disease)

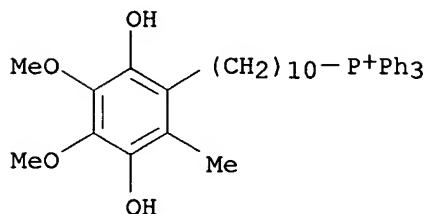
RN 845959-55-9 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 747398-82-9

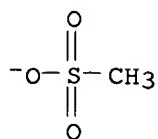
CMF C37 H46 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



L3 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:739270 CAPLUS

DOCUMENT NUMBER: 147:273456

TITLE: Quantitation and metabolism of mitoquinone, a mitochondria-targeted antioxidant, in rat by liquid chromatography/tandem mass spectrometry

AUTHOR(S): Li, Yan; Zhang, Hu; Fawcett, J. Paul; Tucker, Ian G.

CORPORATE SOURCE: School of Pharmacy, University of Otago, Dunedin, N. Z.

SOURCE: Rapid Communications in Mass Spectrometry (2007), 21(13), 1958-1964

CODEN: RCMSEF; ISSN: 0951-4198

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mitoquinone (MitoQ10 mesylate) is a mitochondria-targeted antioxidant undergoing development for the treatment of neurodegenerative diseases. The aim of this study was to develop and validate an assay based on liquid chromatog./tandem mass spectrometry (LC/MS/MS) to determine mitoquinone and to detect and identify the metabolites of MitoQ10 in rat plasma after an oral dose. After a simple protein precipitation step, plasma samples were analyzed by

reversed-phase liquid chromatog. using gradient elution with acetonitrile/water/formic acid. Electrospray ionization in the pos. ion mode with multiple reaction monitoring (MRM) was used to analyze mitoquinone employing the deuterated compound (d3-MitoQ10 mesylate) as internal standard. The calibration curve for mitoquinone was linear over the concentration range 0.5-250 ng/mL with a correlation coefficient >0.995. The method

was sensitive (limit of quantitation 0.5 ng/mL) and had acceptable accuracy (relative error <8.7%) and precision (intra- and inter-day coefficient of variation <12.4%). Recoveries of mitoquinone at concns. of 1.5, 20 and 200 ng/mL were in the range 87-114%. The method was successfully applied to a pharmacokinetic study in rat after a single oral dose in which four metabolites of MitoQ10 were tentatively identified as hydroxylated MitoQ10, desmethyl MitoQ10 and the glucuronide and sulfate conjugates of the quinol form of MitoQ10.

IT 845959-55-9, Mitoquinol

RL: BSU (Biological study, unclassified); BIOL (Biological study) (quantitation and metabolism of mitochondria-targeted antioxidant mitoquinone in rat)

RN 845959-55-9 CAPLUS

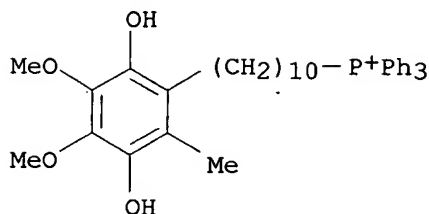
CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 747398-82-9



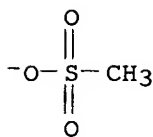
CMF C37 H46 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:407185 CAPLUS

DOCUMENT NUMBER: 147:63256

TITLE: Transport and metabolism of MitoQ10, a mitochondria-targeted antioxidant, in Caco-2 cell monolayers

AUTHOR(S): Li, Yan; Fawcett, J. Paul; Zhang, Hu; Tucker, Ian G.  
CORPORATE SOURCE: School of Pharmacy, University of Otago, Dunedin, N. Z.

SOURCE: Journal of Pharmacy and Pharmacology (2007), 59(4), 503-511

CODEN: JPPMAB; ISSN: 0022-3573

PUBLISHER: Pharmaceutical Press

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 147:63256

AB Mitoquinone (MitoQ10 mesylate) is a mitochondria-targeted antioxidant formulated for oral administration in the treatment of neurodegenerative diseases. We have investigated the absorption and metabolism of MitoQ10 in Caco-2 cell monolayers. The intracellular accumulation of MitoQ10 was 18-41% of the total amount of MitoQ10 added. Some of the intracellular MitoQ10 was reduced to mitoquinol and subsequently metabolized to glucuronide and sulfate conjugates. Transport of MitoQ10 was polarized with the apparent permeability (Papp) from basolateral (BL) to apical (AP) (PappBL→AP) being >2.5-fold the Papp from apical to basolateral (PappAP→BL). In the presence of 4% bovine serum albumin on the basolateral side, the PappAP→BL value increased 7-fold compared with control. The PappBL→AP value decreased by 26%, 31%, and 61%

in the presence of verapamil 100  $\mu\text{M}$ , ciclosporin 10 and 30  $\mu\text{M}$ , resp., whereas the PappAP $\rightarrow$ BL value increased 71% in the presence of ciclosporin 30  $\mu\text{M}$ . Apical efflux of mitoquinol sulfate and mitoquinol glucuronide conjugates was significantly decreased by ciclosporin 30  $\mu\text{M}$  and the breast cancer receptor protein (BCRP) inhibitor, reserpine 25  $\mu\text{M}$ , resp. These results suggested that the bioavailability of MitoQ10 may be limited by intracellular metabolism and the action of P-glycoprotein and BCRP. However, the dramatic increase in absorptive Papp in the presence of bovine serum albumin on the receiver side suggests these barrier functions may be less significant in-vivo.

IT 845959-55-9, Mitoquinol

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(transport and metabolism of MitoQ10 as mitochondria-targeted antioxidant, in Caco-2 cell monolayers)

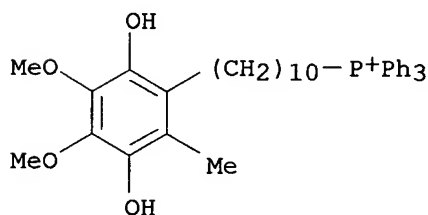
RN 845959-55-9 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 747398-82-9

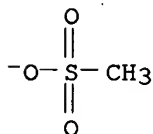
CMF C37 H46 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1067714 CAPLUS

DOCUMENT NUMBER: 145:419306

TITLE: Preparation of mitoquinone derivatives as mitochondrially targeted antioxidants

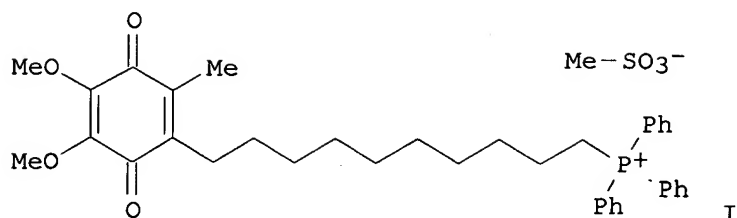
INVENTOR(S): Taylor, Kenneth Martin; Smith, Robin A. J.

PATENT ASSIGNEE(S): Antipodean Pharmaceuticals, Inc., USA

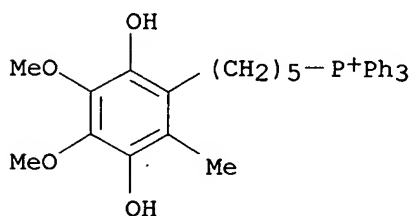
SOURCE: U.S. Pat. Appl. Publ., 57pp., Cont.-in-part of U.S. Ser. No. 172,916.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 5  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060229278	A1	20061012	US 2006-355518	20060215
WO 9926954	A1	19990603	WO 1998-NZ173	19981125
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			NZ 2003-527800	A 20030822
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			US 2003-722542	B1 20031128
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OTHER SOURCE(S): MARPAT 145:419306  
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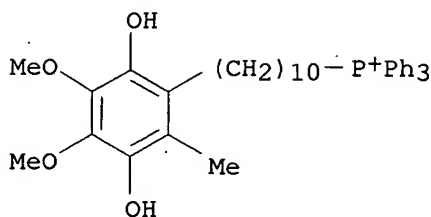


- AB This invention relates to pharmaceutically acceptable amphiphilic antioxidant compds., compns. and dosage forms comprising the compds. The compds., compns., dosage forms, uses and methods are useful in the treatment of diseases or conditions associated with oxidative stress. Thus, I 1:2 complex  $\beta$ -cyclodextrin with was prepared, and tested for stability and pharmacokinetics.
- IT 764723-89-9P 845959-55-9P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)
- RN 764723-89-9 CAPLUS
- CN Phosphonium, [5-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



● I<sup>-</sup>

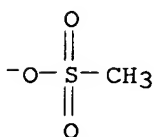
- RN 845959-55-9 CAPLUS
- CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)
- CM 1
- CRN 747398-82-9
- CMF C37 H46 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



L3 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:51133 CAPLUS

DOCUMENT NUMBER: 144:121851

TITLE: Use of mitochondrially targeted antioxidant-lipophilic cation conjugate in the treatment of liver diseases and epithelial cancers.

INVENTOR(S): Froehlich, Eleonore; Kvietikova, Ivica; Zatloukal, Kurt; Schatz, Gottfried; Denk, Helmut; Stumptner, Cornelia; Buck, Charles

PATENT ASSIGNEE(S): Oridis Biomed Forschungs- und Entwicklungs G.m.b.H., Austria

SOURCE: PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006005759	A2	20060119	WO 2005-EP53338	20050712
WO 2006005759	A3	20060511		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,				

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM

AU 2005261654	A1	20060119	AU 2005-261654	20050712
CA 2573456	A1	20060119	CA 2005-2573456	20050712
EP 1765413	A2	20070328	EP 2005-775873	20050712

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,  
 IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

CN 1997403	A	20070711	CN 2005-80023193	20050712
JP 2008506667	T	20080306	JP 2007-520833	20050712
KR 2007030815	A	20070316	KR 2006-725659	20061206
US 20070225255	A1	20070927	US 2007-632149	20070212

PRIORITY APPLN. INFO.: EP 2004-103318 A 20040713  
 WO 2005-EP53338 W 20050712

OTHER SOURCE(S): MARPAT 144:121851

AB The invention discloses the use of a mitochondrially targeted antioxidant, e.g. derivs. of vitamin E, coenzyme Q10 or a glutathione peroxidase mimetic, in the treatment and prevention of liver diseases and/or epithelial cancers. The invention also discloses pharmaceutical compns. containing the antioxidant(s) intended for such use. Furthermore the invention relates to the manufacture of medicaments containing the antioxidant(s)

useful for such prevention and treatment. Compds. of the invention comprise a lipophilic cation covalently coupled to an antioxidant moiety, e.g. (Ph)3P+XR·Z- (X = linking group; R = antioxidant moiety; Z- = anion).

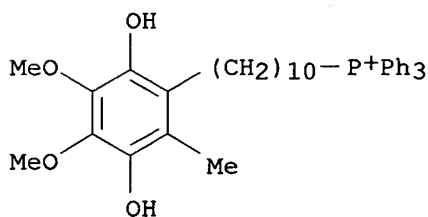
IT 299975-19-2 747398-82-9D, salts 845959-55-9  
 873653-01-1 873653-02-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitochondrially targeted antioxidant-lipophilic cation conjugate for treatment of liver disease and epithelial cancer)

RN 299975-19-2 CAPLUS

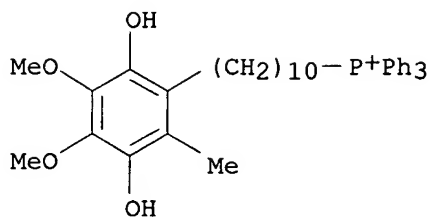
CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

RN 747398-82-9 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl- (CA INDEX NAME)



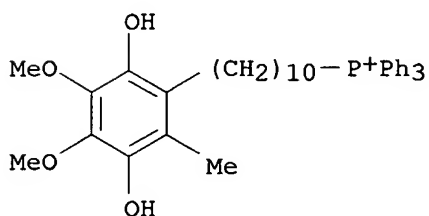
RN 845959-55-9 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 747398-82-9

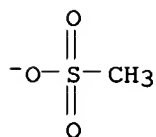
CMF C37 H46 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



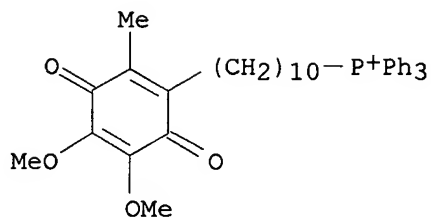
RN 873653-01-1 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide, mixt. with [10-(3,6-dihydroxy-4,5-dimethoxy-2-methylphenyl)decyl]triphenylphosphonium bromide (9CI) (CA INDEX NAME)

CM 1

CRN 336184-91-9

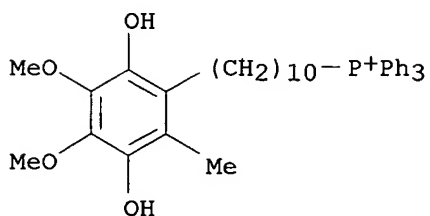
CMF C37 H44 O4 P . Br

● Br<sup>-</sup>

CM 2

CRN 299975-19-2

CMF C37 H46 O4 P . Br

● Br<sup>-</sup>

RN 873653-02-2 CAPLUS

CN Phosphonium, [10-(3,6-dihydroxy-4,5-dimethoxy-2-methylphenyl)decyl]triphenyl-, methanesulfonate, mixt. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 845959-55-9

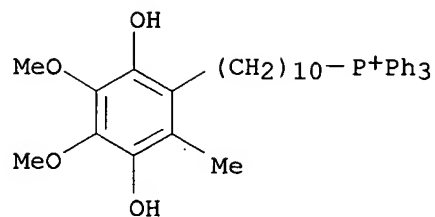
CMF C37 H46 O4 P . C H3 O3 S

CM 2

CRN 747398-82-9

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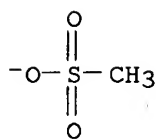




CM 3

CRN 16053-58-0

CMF C H3 O3 S



CM 4

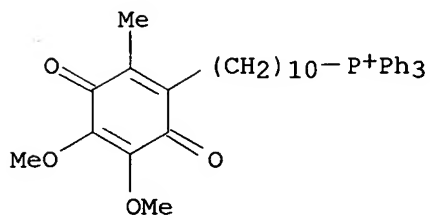
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CMF C37 H44 O4 P . C H3 O3 S

CM 5

CRN 444890-41-9

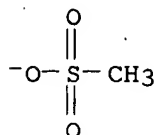
CMF C37 H44 O4 P



CM 6

CRN 16053-58-0

CMF C H3 O3 S



L3 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:182678 CAPLUS

DOCUMENT NUMBER: 142:254662

TITLE: Mitoquinone derivatives used as mitochondrially targeted antioxidants, and preparation thereof

INVENTOR(S): Murphy, Michael Patrick; Smith, Robin

PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.

SOURCE: PCT Int. Appl., 102 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005019233	A1	20050303	WO 2004-NZ197	20040823
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003204144	A1	20030612	AU 2003-204144	20030512
AU 2003204144	B2	20070301		
US 20070238709	A1	20071011	US 2007-568654	20070222
PRIORITY APPLN. INFO.:			NZ 2003-527800	A 20030822
			NZ 2003-529153	A 20031023
			NZ 2004-533555	A 20040614
			AU 1999-16965	A3 19981125
			NZ 1998-329255	A 19981125
			WO 2004-NZ197	W 20040823

OTHER SOURCE(S): CASREACT 142:254662; MARPAT 142:254662

AB This invention discloses methods to screen for, identify, select, and synthesize amphiphilic mitochondrially targeted antioxidant compds., and compns., dosage forms, and methods reliant on these compds. The compds. are all mitoquinone derivs., being methoxyphenyl alkyl triphenylphosphonium or methoxy dioxocyclohexadiene alkyl triphenylphosphonium derivs. The compds., compns., dosage forms and methods are useful in e.g. the treatment of diseases or conditions associated with oxidative stress.

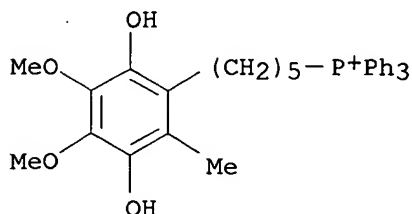
IT 764723-89-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 764723-89-9 CAPLUS

CN Phosphonium, [5-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



● I<sup>-</sup>

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:182677 CAPLUS

DOCUMENT NUMBER: 142:254661

TITLE: Mitoquinone derivatives used as mitochondrially targeted antioxidants, and preparation thereof

INVENTOR(S): Taylor, Kenneth Martin; Smith, Robin

PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.

SOURCE: PCT Int. Appl., 143 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005019232	A1	20050303	WO 2004-NZ196	20040823
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003204144	A1	20030612	AU 2003-204144	20030512
AU 2003204144	B2	20070301		
AU 2004266988	A1	20050303	AU 2004-266988	20040823
CA 2536546	A1	20050303	CA 2004-2536546	20040823
EP 1664069	A1	20060607	EP 2004-775122	20040823
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

CN 1839142	A	20060927	CN 2004-80024155	20040823
BR 2004013742	A	20061024	BR 2004-13742	20040823
JP 2007503387	T	20070222	JP 2006-523805	20040823
US 20060229278	A1	20061012	US 2006-355518	20060215
MX 2006PA02114	A	20061207	MX 2006-PA2114	20060222
NO 2006000977	A	20060519	NO 2006-977	20060228
US 20080161267	A1	20080703	US 2006-568655	20060831
PRIORITY APPLN. INFO.:			NZ 2003-527800	A 20030822
			NZ 2003-529153	A 20031023
			NZ 2004-533556	A 20040614
			AU 1999-16965	A3 19981125
			NZ 1998-329255	A 19981125
			WO 1998-NZ173	A2 19981125
			US 2000-577877	A1 20000525
			US 2001-968838	B1 20011003
			US 2002-272914	B1 20021018
			US 2003-722542	B1 20031128
			WO 2004-NZ196	W 20040823
			US 2005-172916	A2 20050705

OTHER SOURCE(S): CASREACT 142:254661; MARPAT 142:254661

AB The invention discloses pharmaceutically acceptable amphiphilic antioxidant compds., compns., and dosage forms comprising these compds., and methods and uses reliant on these compds. The compds. are all mitoquinone derivs., being methoxyphenyl alkyl triphenylphosphonium or methoxy dioxocyclohexadiene alkyl triphenylphosphonium derivs. The compds., compns., dosage forms, uses, and methods are useful in e.g. the treatment of diseases or conditions associated with oxidative stress.

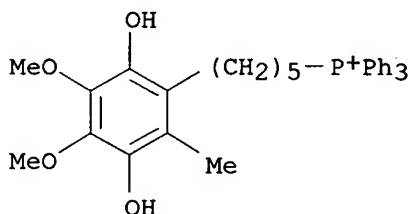
IT 764723-89-9P 845959-55-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 764723-89-9 CAPLUS

CN Phosphonium, [5-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



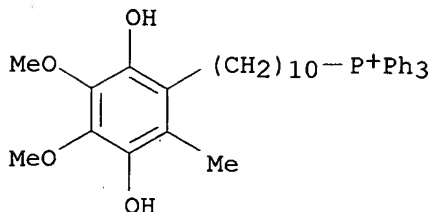
● I<sup>-</sup>

RN 845959-55-9 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

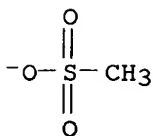
CM 1

CRN 747398-82-9  
CMF C37 H46 O4 P



CM 2

CRN 16053-58-0  
CMF C H3 O3 S



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:601038 CAPLUS

DOCUMENT NUMBER: 141:290668

TITLE: Fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant

AUTHOR(S): Asin-Cayuela, Jordi; Manas, Abdul-Rahman B.; James, Andrew M.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Wellcome Trust/MRC Building, Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK

SOURCE: FEBS Letters (2004), 571(1-3), 9-16

CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 141:290668

AB The mitochondria-targeted antioxidant MitoQ comprises a ubiquinol moiety covalently attached through an aliphatic carbon chain to the lipophilic triphenylphosphonium cation. This cation drives the membrane potential-dependent accumulation of MitoQ into mitochondria, enabling the ubiquinol antioxidant to prevent mitochondrial oxidative damage far more effectively than untargeted antioxidants. We sought to fine-tune the hydrophobicity of MitoQ so as to control the extent of its membrane binding and penetration into the phospholipid bilayer, and thereby regulate its partitioning between the membrane and aqueous phases within mitochondria and cells. To do this, MitoQ variants with 3, 5, 10 and 15 carbon aliphatic chains were synthesized. These mols. had a wide range of hydrophobicities with octan-1-ol/phosphate buffered saline partition

coeffs. from 2.8 to 20,000. All MitoQ variants were accumulated into mitochondria driven by the membrane potential, but their binding to phospholipid bilayers varied from negligible for MitoQ3 to essentially total for MitoQ15. Despite the span of hydrophobicities, all MitoQ variants were effective antioxidants. Therefore, it is possible to fine-tune the degree of membrane association of MitoQ and other mitochondria targeted compds., without losing antioxidant efficacy. This indicates how the uptake and distribution of mitochondria-targeted compds. within mitochondria and cells can be controlled, thereby facilitating investigations of mitochondrial oxidative damage.

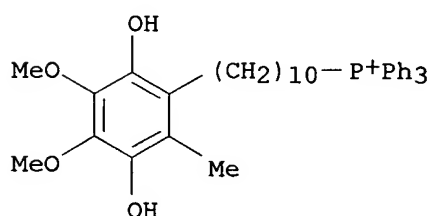
IT 299975-19-2

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(preparation of MitoQ variants for fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant)

RN 299975-19-2 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

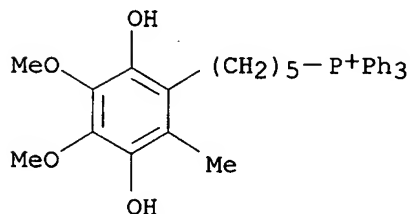
IT 764723-89-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of MitoQ variants for fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant)

RN 764723-89-9 CAPLUS

CN Phosphonium, [5-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



● I<sup>-</sup>

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:368168 CAPLUS

DOCUMENT NUMBER: 139:106294

TITLE: Delivery of bioactive molecules to mitochondria in vivo

AUTHOR(S): Smith, Robin A. J.; Porteous, Carolyn M.; Gane, Alison M.; Murphy, Michael P.

CORPORATE SOURCE: Department of Chemistry, University of Otago, Dunedin, N. Z.

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(9), 5407-5412  
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

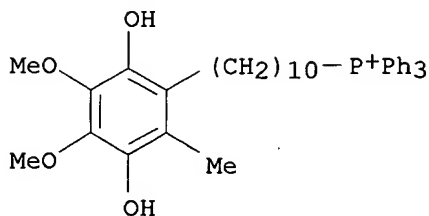
AB Mitochondrial dysfunction contributes to many human degenerative diseases but specific treatments are hampered by the difficulty of delivering bioactive mols. to mitochondria in vivo. To overcome this problem we developed a strategy to target bioactive mols. to mitochondria by attachment to the lipophilic triphenylphosphonium cation through an alkyl linker. These mols. rapidly permeate lipid bilayers and, because of the large mitochondrial membrane potential (neg. inside), accumulate several hundredfold inside isolated mitochondria and within mitochondria in cultured cells. To determine whether this strategy could lead to the development of mitochondria-specific therapies, we investigated the administration and tissue distribution in mice of simple alkyltriphenylphosphonium cations and of mitochondria-targeted antioxidants comprising a triphenylphosphonium cation coupled to a coenzyme Q or vitamin E derivative. Significant doses of these compds. could be fed safely to mice over long periods, coming to steady-state distributions within the heart, brain, liver, and muscle. Therefore, mitochondria-targeted bioactive mols. can be administered orally, leading to their accumulation at potentially therapeutic concns. in those tissues most affected by mitochondrial dysfunction. This finding opens the way to the testing of mitochondria-specific therapies in mouse models of human degenerative diseases.

IT 299975-19-2

RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(bioactive mols. delivery to mitochondria in vivo)

RN 299975-19-2 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

● Br<sup>-</sup>

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:154438 CAPLUS

DOCUMENT NUMBER: 138:187926

TITLE: Preparation of triphenylphosphonium quinols and quinones

INVENTOR(S): Smith, Robin; Murphy, Michael Patrick

PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.

SOURCE: PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

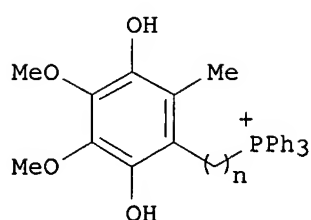
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

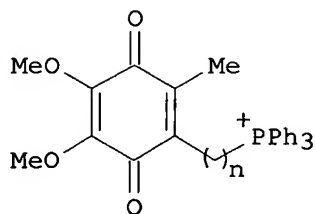
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003016323	A1	20030227	WO 2002-NZ154	20020812
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
NZ 513547	A	20020927	NZ 2001-513547	20010813
AU 2002326242	A1	20030303	AU 2002-326242	20020812
EP 1423396	A1	20040602	EP 2002-760924	20020812
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			
US 20050043553	A1	20050224	US 2004-486797	20041001
US 7179928	B2	20070220		
PRIORITY APPLN. INFO.:			NZ 2001-513547	A 20010813
			WO 2002-NZ154	W 20020812
OTHER SOURCE(S):	CASREACT 138:187926; MARPAT 138:187926			
GI				





I



II

AB Triphenylphosphonium quinols and quinones [e.g., I and II, resp.; wherein  $n$  = integer from 6 to 40] were prepared. For example, Idebenone is reacted with  $\text{PPh}_3$  and  $\text{PPh}_3 \cdot \text{HBr}$  to give 57% MitoQuinol I  $\text{Br}^-$  ( $n = 10$ ), which is purified and oxidized with  $\text{H}_2\text{O}_2/\text{pyridine}$  to give 77% MitoQuinone II  $\text{Br}^-$  ( $n = 10$ ).

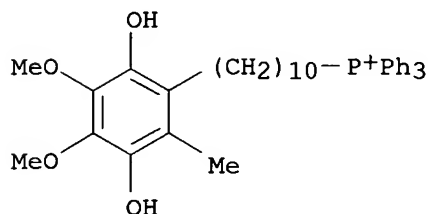
IT 299975-19-2P

RL: IMF (Industrial manufacture); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of triphenylphosphonium quinols and quinones)

RN 299975-19-2 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



●  $\text{Br}^-$

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:137933 CAPLUS

DOCUMENT NUMBER: 134:322127

TITLE: Selective targeting of a redox-active ubiquinone to mitochondria within cells. Antioxidant and antiapoptotic properties

AUTHOR(S): Kelso, Geoffrey F.; Porteous, Carolyn M.; Coulter, Carolyn V.; Hughes, Gillian; Porteous, William K.; Ledgerwood, Elizabeth C.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Department of Chemistry, University of Otago, Dunedin, N. Z.

SOURCE: Journal of Biological Chemistry (2001), 276(7),

4588-4596

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER:

American Society for Biochemistry and Molecular  
Biology

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 134:322127

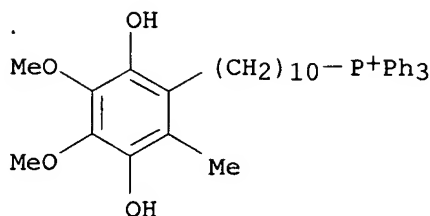
AB With the recognition of the central role of mitochondria in apoptosis, there is a need to develop specific tools to manipulate mitochondrial function within cells. Here we report on the development of a novel antioxidant that selectively blocks mitochondrial oxidative damage, enabling the roles of mitochondrial oxidative stress in different types of cell death to be inferred. This antioxidant, named mitoQ, is a ubiquinone derivative targeted to mitochondria by covalent attachment to a lipophilic triphenylphosphonium cation through an aliphatic carbon chain. Due to the large mitochondrial membrane potential, the cation was accumulated within mitochondria inside cells, where the ubiquinone moiety inserted into the lipid bilayer and was reduced by the respiratory chain. The ubiquinol derivative thus formed was an effective antioxidant that prevented lipid peroxidn. and protected mitochondria from oxidative damage. After detoxifying the reactive oxygen species peroxynitrite, the ubiquinol moiety was regenerated by the respiratory chain enabling its antioxidant activity to be recycled. In cell culture studies, the mitochondrially localized antioxidant protected mammalian cells from hydrogen peroxide-induced apoptosis but not from apoptosis induced by staurosporine or tumor necrosis factor- $\alpha$ . This was compared with untargeted ubiquinone analogs, which were ineffective in preventing apoptosis. These results suggest that mitochondrial oxidative stress may be a critical step in apoptosis induced by hydrogen peroxide but not for apoptosis induced by staurosporine or tumor necrosis factor- $\alpha$ . We have shown that selectively manipulating mitochondrial antioxidant status with targeted and recyclable antioxidants is a feasible approach to investigate the role of mitochondrial oxidative damage in apoptotic cell death. This approach will have further applications in investigating mitochondrial dysfunction in a range of exptl. models.

IT 299975-19-2P

RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)  
(novel redox-active ubiquinone mitoQ displays antioxidant and antiapoptotic properties in mitochondria)

RN 299975-19-2 CAPLUS

CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



●  $\text{Br}^-$

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:531391 CAPLUS

DOCUMENT NUMBER: 133:280110

TITLE: Mitochondrially targeted antioxidants and thiol reagents

AUTHOR(S): Coulter, C. V.; Kelso, G. F.; Lin, T.-K.; Smith, R. A. J.; Murphy, M. P.

CORPORATE SOURCE: University of Otago, Dunedin, N. Z.

SOURCE: Free Radical Biology & Medicine (2000), 28(10), 1547-1554

CODEN: FRBMEH; ISSN: 0891-5849

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

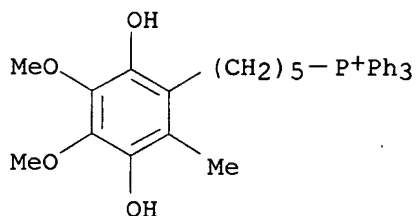
AB Mitochondrial oxidative damage and dysfunction contributes to a number of cell pathologies. To investigate how this damage affects cell function we have developed mitochondrially targeted antioxidants and thiol reagents by covalently linking them to lipophilic cations. The cation drives the selective accumulation of these reagents into mitochondria within cells where the antioxidants decrease oxidative damage and the thiol reagents enable measurement of the redox status of thiol proteins. In conjunction with cell and animal models of apoptosis, oxidative damage, and nitric oxide signaling, these mols. may provide new insights into the roles of mitochondria in human pathologies.

IT 299975-18-1P 299975-19-2P

RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(mitochondrially targeted antioxidants and thiol reagents)

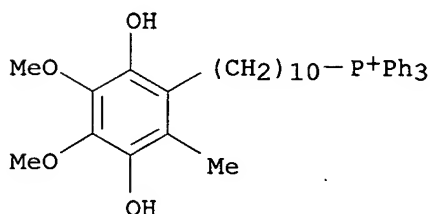
RN 299975-18-1 CAPLUS

CN Phosphonium, [5-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)pentyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

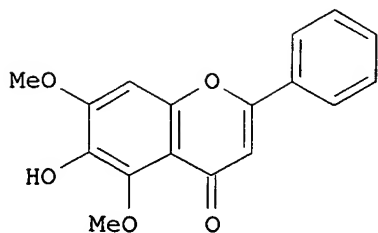
RN 299975-19-2 CAPLUS  
 CN Phosphonium, [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



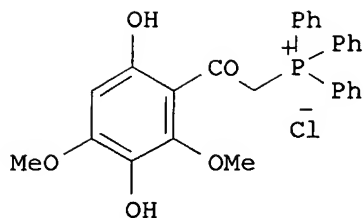
● Br<sup>-</sup>

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN  
 ACCESSION NUMBER: 1999:171401 CAPLUS  
 DOCUMENT NUMBER: 130:296524  
 TITLE: A novel route to 5,7-dimethoxy-6-hydroxyflavone  
 AUTHOR(S): Osorio-Olivares, Mauricio; Cassels, Bruce K.;  
 Sepulveda-Boza, Silvia; Rezende, Marcos Caroli  
 CORPORATE SOURCE: Facultad de Quimica y Biologia, Universidad de  
 Santiago de Chile, Santiago, 3363, Chile  
 SOURCE: Synthetic Communications (1999), 29(5), 815-819  
 CODEN: SYNCAV; ISSN: 0039-7911  
 PUBLISHER: Marcel Dekker, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 130:296524  
 GI



I



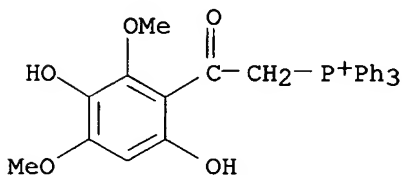
II

AB A novel synthetic route to 5,7-dimethoxy-6-hydroxyflavone (I) was described which involved the cyclization of phosphorane II with benzoyl chloride as the key step.

IT 223409-64-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis of 5,7-dimethoxy-6-hydroxyflavone via phosphorane cyclization)

RN 223409-64-1 CAPLUS

CN Phosphonium, [2-(3,6-dihydroxy-2,4-dimethoxyphenyl)-2-oxoethyl]triphenyl-, chloride (1:1) (CA INDEX NAME)



● Cl<sup>-</sup>

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1987:57931 CAPLUS

DOCUMENT NUMBER: 106:57931

ORIGINAL REFERENCE NO.: 106:9451a,9454a

TITLE: Spectroscopic studies of organophosphorus compounds. Part XI. Preparation and IR spectra of phosphobetaine tetrachlorocobaltates

AUTHOR(S): Beg, M. Arshad A.; Siddiqui, M. Siddique

CORPORATE SOURCE: PCSIR Lab., Karachi, Pak.

SOURCE: Pakistan Journal of Scientific and Industrial Research (1986), 29(3), 165-71

CODEN: PSIRAA; ISSN: 0030-9885

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Tetrachlorocobaltates of phosphobetaine from triarylphosphines and p-quinones were prepared to study the result of interaction of a bulky anion. Phosphobetaine tetrachlorocobaltates were prepared either by the

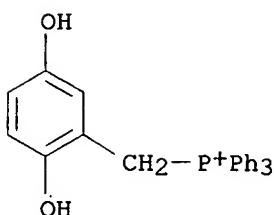
interaction of  $\text{CoCl}_2$  with phosphobetaine or phosphobetaine hydrochloride. A comparison of the known spectra of phosphonium iodide, bromide and their tetrachlorocobaltates with those of phosphobetaine hydrochloride and their tetrachlorocobaltates indicates that the intensity of the IR bands as well as their positions are affected on charging the halides into tetrachlorocobaltates. There is a significant (4-5 fold) enhancement in intensity and some of the bands like the k and l modes, which are otherwise unresolved, are well separated. The O mode behaves as an X-sensitive mode and is shifted to a higher frequency.

IT 105415-88-1P 105415-90-5P 105832-05-1P  
105847-81-2P

RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
(preparation and IR spectra of)

RN 105415-88-1 CAPLUS

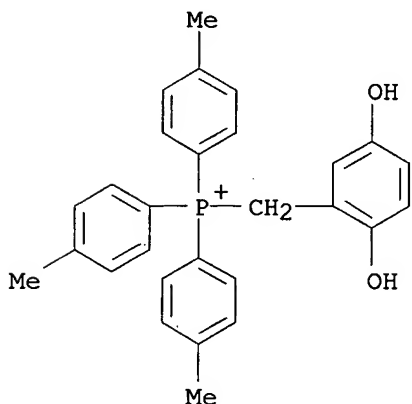
CN Phosphonium, [(2,5-dihydroxyphenyl)methyl]triphenyl-, chloride (9CI) (CA INDEX NAME)



●  $\text{Cl}^-$

RN 105415-90-5 CAPLUS

CN Phosphonium, [(2,5-dihydroxyphenyl)methyl]tris(4-methylphenyl)-, chloride (9CI) (CA INDEX NAME)



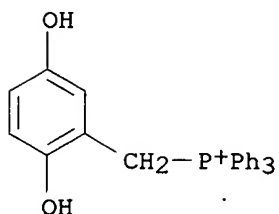
●  $\text{Cl}^-$

RN 105832-05-1 CAPLUS

CN Phosphonium, [(2,5-dihydroxyphenyl)methyl]triphenyl-, (T-4)-  
tetrachlorocobaltate(2-) (2:1) (CA INDEX NAME)

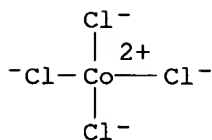
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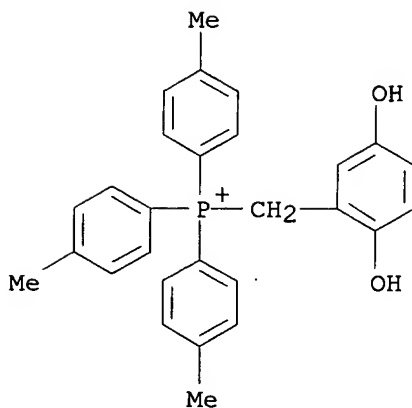
CRN 14337-08-7  
CMF Cl4 Co  
CCI CCS



RN 105847-81-2 CAPLUS  
CN Phosphonium, [(2,5-dihydroxyphenyl)methyl]tris(4-methylphenyl)-,  
(T-4)-tetrachlorocobaltate(2-) (2:1) (CA INDEX NAME)

CM 1

CRN 105847-80-1  
CMF C28 H28 O2 P

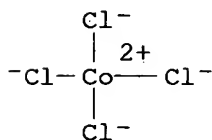


CM 2

CRN 14337-08-7

CMF C14 Co

CCI CCS



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TOTAL

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NEWS	16	MAR 31	CA/Caplus and CASREACT patent number format for U.S. applications updated
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NEWS	20	APR 15	WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS	21	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS	22	APR 28	IMSRESEARCH reloaded with enhancements
NEWS	23	MAY 30	INPAFAMDB now available on STN for patent family searching
NEWS	24	MAY 30	DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
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NEWS	26	JUN 06	KOREAPAT updated with 41,000 documents
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NEWS	28	JUN 19	CAS REGISTRY includes selected substances from web-based collections
NEWS	29	JUN 25	CA/Caplus and USPAT databases updated with IPC reclassification data

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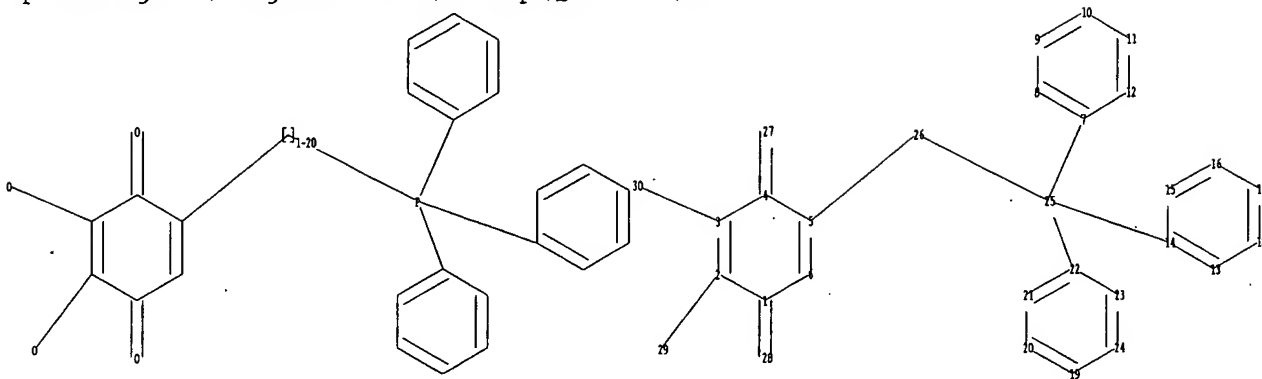
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chain nodes :

25 26 27 28 29 30

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

chain bonds :

1-28 2-29 3-30 4-27 5-26 7-25 14-25 22-25 25-26

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-18 14-15 15-16 16-17 17-18 19-20 19-24 20-21 21-22 22-23 23-24

exact/norm bonds :

1-2 1-6 1-28 2-3 2-29 3-4 3-30 4-5 4-27 5-6

exact bonds :

5-26 7-25 14-25 22-25 25-26

normalized bonds :

7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-18 14-15 15-16 16-17 17-18 19-20 19-24 20-21 21-22 22-23 23-24

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom  
 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom  
 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS  
 29:CLASS 30:CLASS

L1 STRUCTURE UPLOADED

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FULL SCREEN SEARCH COMPLETED - 142 TO ITERATE

100.0% PROCESSED 142 ITERATIONS  
 SEARCH TIME: 00.00.01

21 ANSWERS

L2 21 SEA SSS FUL L1

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L3 35 L2

=&gt; D L3 IBIB ABS HITSTR 1-35

L3 ANSWER 1 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:459952 CAPLUS

DOCUMENT NUMBER: 149:47117

TITLE: Rapid and extensive uptake and activation of hydrophobic triphenylphosphonium cations within cells  
AUTHOR(S): Ross, Meredith F.; Prime, Tracy A.; Abakumova, Irina; James, Andrew M.; Porteous, Carolyn M.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Wellcome Trust/MRC Building, Medical Research Council  
Dunn Human Nutrition Unit, Cambridge, CB2 0XY, UK

SOURCE: Biochemical Journal (2008), 411(3), 633-645

CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mitochondria-targeted mols. comprising the lipophilic TPP (triphenylphosphonium) cation covalently linked to a hydrophobic bioactive moiety are used to modify and probe mitochondria in cells and in vivo. However, it is unclear how hydrophobicity affects the rate and extent of

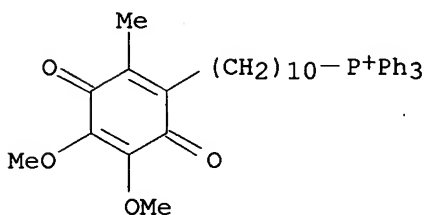
their uptake into mitochondria within cells, making it difficult to interpret expts. because their intracellular concentration in different compartments is uncertain. To address this issue, we compared the uptake into both isolated mitochondria and mitochondria within cells of two hydrophobic TPP derivs., [3H]MitoQ (mitoquinone) and [3H]DecylTPP, with the more hydrophilic TPP cation [3H]TPMP (methyltriphenylphosphonium). Uptake of MitoQ by mitochondria and cells was described by the Nernst equation and was .apprx.5-fold greater than that for TPMP, as a result of its greater binding within the mitochondrial matrix. DecylTPP was also taken up extensively by cells, indicating that increased hydrophobicity enhanced uptake. Both MitoQ and DecylTPP were taken up very rapidly into cells, reaching a steady state within 15 min, compared with .apprx.8 h for TPMP. This far faster uptake was the result of the increased rate of passage of hydrophobic TPP mols. through the plasma membrane. Within cells MitoQ was predominantly located within mitochondria, where it was rapidly reduced to the ubiquinol form, consistent with its protective effects in cells and in vivo being due to the ubiquinol antioxidant. The strong influence of hydrophobicity on TPP cation uptake into mitochondria within cells facilitates the rational design of mitochondria-targeted compds. to report on and modify mitochondrial function in vivo.

IT 444890-41-9, Mitoquinone

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(rapid and extensive uptake and activation of hydrophobic triphenylphosphonium cations within cells)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT:

44

THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:352859 CAPLUS

DOCUMENT NUMBER: 148:394354

TITLE: Compositions and methods for treatment of viral diseases

INVENTOR(S): Johansen, Lisa M.; Owens, Christopher M.; Mawhinney, Christina; Chappell, Todd W.; Brown, Alexander T.; Frank, Michael G.; Altmeyer, Ralf

PATENT ASSIGNEE(S): Combinatorx (Singapore) Pre. Ltd., Singapore

SOURCE: PCT Int. Appl., 237pp.

CODEN: PIXXD2

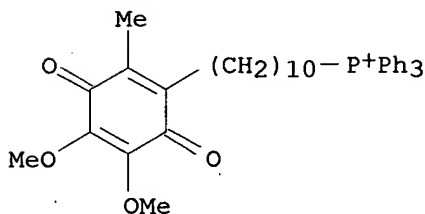
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

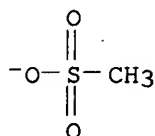
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008033466	A2	20080320	WO 2007-US19932	20070913
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20080161324	A1	20080703	US 2007-900893	20070913
PRIORITY APPLN. INFO.:			US 2006-844463P	P 20060914
			US 2006-874061P	P 20061211
AB	Based on the results of the authors screen identifying compds. and combinations of compds. having antiviral activity, the present invention features compns., methods, and kits useful in the treatment of viral diseases. In certain embodiments, the viral disease is caused by a single stranded RNA virus, a flaviviridae virus, or a hepatic virus. In particular embodiments, the viral disease is viral hepatitis (e.g., hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E). Also featured are screening methods for identification of novel compds. that may be used to treat a viral disease.			
IT	845959-50-4, Mitoquinone RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (compns. and methods for treatment of viral diseases)			
RN	845959-50-4 CAPLUS			
CN	Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)			
CM	1			
CRN	444890-41-9			
CMF	C37 H44 O4 P			



CM 2

CRN 16053-58-0

CMF C H3 O3 S



L3 ANSWER 3 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:199007 CAPLUS

DOCUMENT NUMBER: 149:26511

TITLE: Interactions of positively charged ubiquinone analog (MitoQ10) with DT-diaphorase in liver mitochondria

AUTHOR(S): Kargin, V. I.; Motovilov, K. A.; Vysokikh, M. Yu.; Yaguzhinskii, L. S.

CORPORATE SOURCE: A. N. Belozerskii Scientific-Research Institute of Physico-Chemical Biology, M. V. Lomonosov Moscow State University, Moscow, 119991, Russia

SOURCE: Biologicheskie Membrany (2008), 25(1), 34-40  
CODEN: BIMEE9; ISSN: 0233-4755

PUBLISHER: Izdatel'stvo Nauka

DOCUMENT TYPE: Journal

LANGUAGE: Russian

AB MitoQ - a pos. charged analog of CoQ - has been studied as an electron transport cofactor in liver mitochondria. NADH-dependent DT-diaphorase is able to reduce MitoQ at a high rate. MitoQH2 in the presence of malate can restore an electron flow from NADH to oxygen blocked by rotenone. Respiration restored by MitoQ is blocked by dicumarol, mixothiazol, and antimycin A. Therefore, in the presence of MitoQ the following electron transport chain is operating in mitochondria: NADH → DT-diaphorase → MitoQ → complex III → complex IV → oxygen.

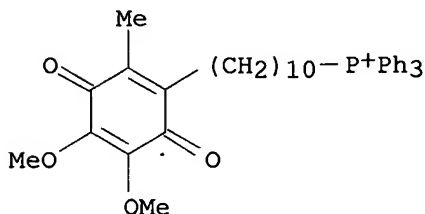
It is shown also that MitoQH2 in the presence of malate (but not succinate) reduces oxygen in the o-center of mitochondrial bcl-complex giving superoxide anion. This reactive oxygen species induces opening of non-specific pore, which leads to the block of oxidative phosphorylation. The data obtained allow considering MitoQ as an analog of hydrophilic quinones, such as duroquinone and K3, which are well-known substrates of DT-diaphorase, but not as an analog of a natural ubiquinone.

IT 444890-41-9

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(vinteractions of pos. charged ubiquinone analog (MitoQ10) with DT-diaphorase in liver mitochondria)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



L3 ANSWER 4 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:164099 CAPLUS

DOCUMENT NUMBER: 148:206611

TITLE: Methods for reducing anthracycline-induced toxicity

INVENTOR(S): Kalyanaraman, Balaraman; Kalivendi, Shasi Vardhan; Joseph, Joy

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 21pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080032940	A1	20080207	US 2007-834799	20070807
PRIORITY APPLN. INFO.:			US 2006-836247P	P 20060807

AB Methods for treating cancers/tumors include administering to a subject an effective amount of a mitochondria-targeted antioxidant alone or in combination with a chemotherapeutic agents. Likewise, methods for mitigating toxicity associated with a chemotherapeutic agent include administering an effective amount of a mitochondria-targeted antioxidant with a single or with multiple chemotherapeutic agents. The invention relates more particularly to coadministering a mitochondria-targeted antioxidant with a chemotherapeutic agent to attenuate the agent's toxicity to normal cells and to enhance its toxicity to tumor cells. At low micromolar concns., mitochondria-targeted antioxidant MitoQ differentially affected normal cells and tumor cells. MitoQ synerized with doxorubicin (DOX) to enhance caspase-3 activity in tumor cell lines (MCF-7, MCF-10A and SH-SY5Y), but not in normal cells lines (CM and 1-19c2). In fact, MitoQ attenuated DOX-induced caspase-3 activity in normal cell lines.

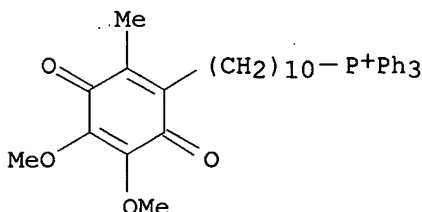
IT 444890-41-9P, MitoQ

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(as mitochondria-targeted antioxidant; reducing anthracycline-induced toxicity by coadministering mitochondria-targeted antioxidant)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



IT 336184-91-9

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

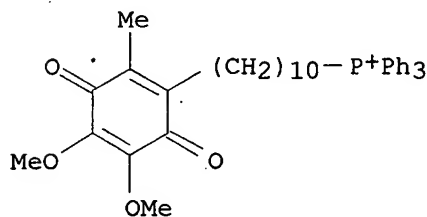
(as mitochondria-targeted antioxidant; reducing anthracycline-induced



toxicity by coadministering mitochondria-targeted antioxidant)

RN 336184-91-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

L3 ANSWER 5 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:90893 CAPLUS

DOCUMENT NUMBER: 148:192198

TITLE: Preparation of peptidomimetics as modulators of pharmacokinetic properties of therapeutics by inhibiting cytochrome P450 monooxygenase

INVENTOR(S): Desai, Manoj C.; Hong, Allen Yu; Liu, Hongtao; Xu, Lianhong; Vivian, Randall W.

PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA

SOURCE: PCT Int. Appl., 346pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

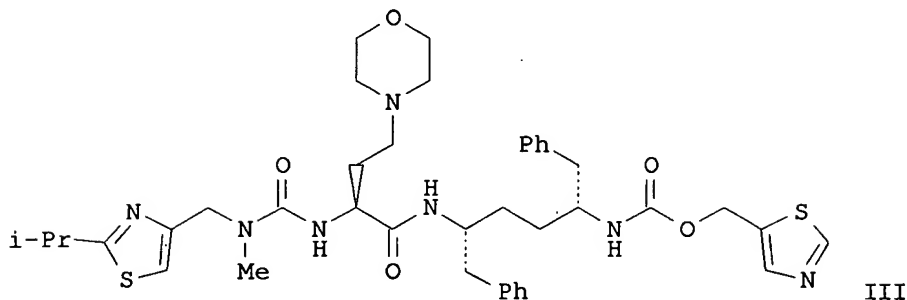
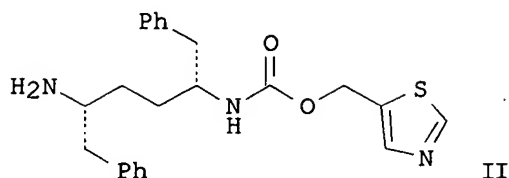
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008010921	A2	20080124	WO 2007-US15604	20070706
WO 2008010921	A3	20080710		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
US 20080108617	A1	20080508	US 2007-825605	20070706
PRIORITY APPLN. INFO.:			US 2006-819315P	P 20060707
			US 2006-832371P	P 20060721
			US 2007-903228P	P 20070223
OTHER SOURCE(S):		MARPAT 148:192198		

GI



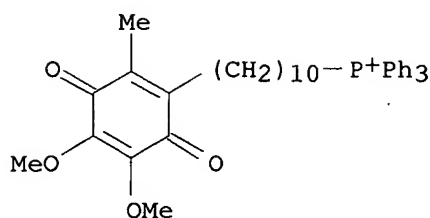
AB The invention is related to the preparation of  $R_8Y_2Z_1[CONR_1(CR_2R_2)_m]nL_1NR_3CH[L_3A(L_4Ar)p]CHR_4L_2CH[L_3A(L_4Ar)p]NR_5CO_2Z_2XR_9$  [I;  $L_1 = C(R_6)_2$ , CO, SO<sub>2</sub>, NHCO and derivs., OCO;  $R_4, R_6 =$  independently H, heteroalkyl, (un)substituted alkyl;  $L_2 =$  a covalent bond,  $C(R_6)_2$ , CO; each  $L_3 =$  independently a covalent bond, (un)substituted alkylene; each  $L_4 = L_3$ , O, CH<sub>2</sub>O, NH; each A = H, (un)substituted alkyl, aryl, heterocyclyl with the proviso that when A = H,  $p = 0$ ;  $Z_1, Z_2 =$  independently O, NH and derivs.; Y, X = independently heterocyclyl, heterocyclylalkyl; each Ar = independently (un)substituted (hetero)aryl;  $R_1, R_3, R_5 =$  independently H, (un)substituted aryl/alkyl; each  $R_2 =$  independently H, (un)substituted arylhetero/hydroxy/amino/alkyl, alkylene-CO<sub>2</sub>H, alkylene-CO-alkyl, etc.;  $R_8, R_9$  are each one or more H's or substituents selected from Cl, CN, (un)substituted alkyl, aryl, heterocyclyl;  $m = 1-2$ ;  $n = 0-1$ ; each  $p =$  independently 0-1], their pharmaceutically acceptable salts, solvates and esters, and compns. containing them which improve the pharmacokinetics of a co-administered drug which is metabolized by cytochrome P 450 monooxygenase. Thus, a multi-step synthesis using 2-isopropyl-4-[(methylamino)methyl]-1,3-thiazole, (2S)-2-amino-4-[(tert-butoxycarbonyl)amino]butanoic acid Me ester, amine II and (BrCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O was given for III. III inhibited CYP450 3A4 (IC<sub>50</sub> = 80-150 nM), CYP450 2C9 (IC<sub>50</sub> = 1,000-10,000 nM) and protease (EC<sub>50</sub> > 20,000 nM in an anti HIV-1 cell culture assay). I alone or in combination with one or more addnl. therapeutic agents which are metabolized by cytochrome P 450 monooxygenase are useful for treating a viral infection, e.g. HIV (no data).

IT 444890-41-9, MitoQ

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(compds. as modulators of pharmacokinetic properties of therapeutic agents)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



L3 ANSWER 6 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:62861 CAPLUS

DOCUMENT NUMBER: 148:182855

TITLE: Is Antioxidant Potential of the Mitochondrial Targeted Ubiquinone Derivative MitoQ Conserved in Cells Lacking mtDNA?

AUTHOR(S): Lu, Chao; Zhang, Dawei; Whiteman, Matthew; Armstrong, Jeffrey S.

CORPORATE SOURCE: Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

SOURCE: Antioxidants & Redox Signaling (2008), 10(3), 651-660  
CODEN: ARSIF2; ISSN: 1523-0864

PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB MitoQ was developed as a mitochondrial targeted antioxidant for diseases associated with oxidative stress. Here we show that MitoQ blocks the generation of reactive oxygen species (ROS) and mitochondrial protein thiol oxidation, and preserves mitochondrial function and ultrastructure after glutathione (GSH) depletion. Furthermore, the antioxidant effect of MitoQ is conserved in cells lacking mitochondrial DNA, indicating that its antioxidant properties do not depend on a functional electron transport chain (ETC). Our results elucidate the antioxidant mechanism of MitoQ and suggest that it may be a useful therapeutic for disorders associated with a dysfunctional ETC and increased ROS production

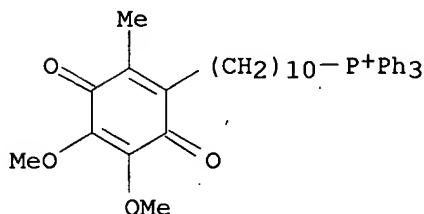
IT 444890-41-9, MitoQ

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(MitoQ antioxidant effect via blocking ROS and protein thiol oxidation, and preserving mitochondria independently of glutathione and electron transport chain)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:40914 CAPLUS

DOCUMENT NUMBER: 148:168504

TITLE: Preparation of purine and thiadeazapurine phosphonate derivatives as modulators of toll-like receptor 7

INVENTOR(S): Chong, Lee S.; Desai, Manoj C.; Gallagher, Brian; Graupe, Michael; Halcomb, Randall L.; Yang, Hong; Zhang, Jennifer R.

PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA

SOURCE: PCT Int. Appl., 273pp.

CODEN: PIXXD2

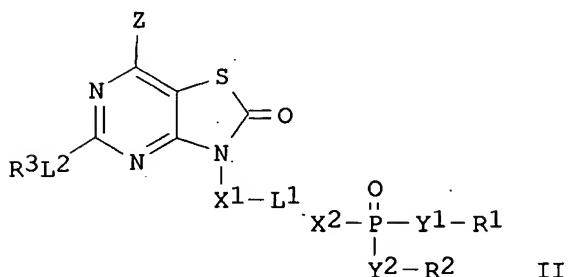
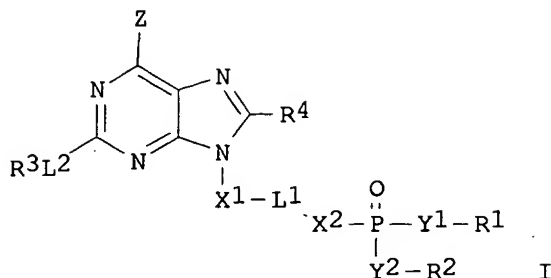
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008005555	A1	20080110	WO 2007-US15615	20070706
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
US 20080008682	A1	20080110	US 2007-825377	20070706
PRIORITY APPLN. INFO.:			US 2006-819490P	P 20060707
			US 2006-832851P	P 20060724
OTHER SOURCE(S):	MARPAT 148:168504			
GI				



AB The present application provides for a compound I [Z = OH, NH<sub>2</sub>; X<sub>1</sub> = (un)substituted alkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene; L<sub>1</sub> = bond, (un)substituted arylene, heterocyclylene, carbocyclylene, S, S(:O), SO<sub>2</sub>, NR<sub>5</sub>, O; X<sub>2</sub> = bond, (un)substituted alkylene; L<sub>2</sub> = NR<sub>5</sub>, NR<sub>5</sub>C(:O), O, S, S(:O), SO<sub>2</sub>, bond; R<sub>3</sub> = H, (un)substituted alkyl, heteroalkyl, alkenyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; Y<sub>1</sub>, Y<sub>2</sub> = bond, O, NR<sub>5</sub>, Y<sub>1</sub>R<sub>1</sub>, Y<sub>2</sub>R<sub>2</sub> = ON:CR<sub>6</sub>R<sub>7</sub>; R<sub>1</sub>, R<sub>2</sub> = H, (un)substituted alkyl, carbocyclyl, heterocyclyl, alkenyl, alkynyl, arylalkyl, etc.; R<sub>4</sub> = H, halogen, OH, O-alkyl, O-alkylene-OCO<sub>2</sub>R<sub>5</sub>, OCO<sub>2</sub>R<sub>5</sub>, SH, NHR<sub>5</sub>; R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> = H, (un)substituted alkyl, carbocyclyl, heterocyclyl, alkenyl, alkynyl, arylalkyl, heterocyclylalkyl, etc.] or II or a pharmaceutically acceptable salt, solvate, and/or ester thereof, compns. containing such compds., therapeutic methods that include the administration of such compds., and therapeutic methods that include the administration of such compds. with at least one addnl. active agent. Thus, [(3-((6-amino-8-hydroxy-2-(2-methoxyethoxy)-9H-purin-9-yl)methyl)phenyl)methyl](methyl)phosphinic acid [I; Z = NH<sub>2</sub>, R<sub>4</sub> = OH, L<sub>2</sub> = O, R<sub>3</sub> = CH<sub>2</sub>CH<sub>2</sub>OMe, X<sub>1</sub> = X<sub>2</sub> = CH<sub>2</sub>, L<sub>1</sub> = 1,3-phenylene, Y<sub>1</sub>R<sub>1</sub> = Me, Y<sub>2</sub>R<sub>2</sub> = OH] was prepared from 6-chloroadenine via N-alkylation with 3-(BrCH<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>Me, alkoxylation with MeOCH<sub>2</sub>CH<sub>2</sub>OH, reesterification with MeI, bromination with Br<sub>2</sub>, Dibal-H reduction, methanolysis with NaOMe/MeOH, acid hydrolysis, bromination with PBr<sub>3</sub>, phosphorylation with MeP(OEt)<sub>2</sub> and acid hydrolysis under microwave irradiation. The toll-like receptor 7 modulating activity of I and II were investigated (no data).

IT 444890-41-9, MitoQ

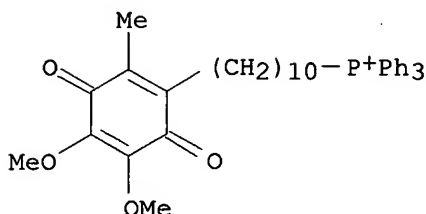
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(compds. as modulators of Toll-like receptor 7 useful in combination therapy and prevention of TLR7 activation-related diseases)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-

yl)decyl]triphenyl- (CA INDEX NAME)



L3 ANSWER 8 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:1220757 CAPLUS

DOCUMENT NUMBER: 148:2715

TITLE: Mitochondrial redox cycling of mitoquinone leads to superoxide production and cellular apoptosis

AUTHOR(S): Doughan, Abdulrahman K.; Dikalov, Sergey I.

CORPORATE SOURCE: Free Radical in Medicine Core, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

SOURCE: Antioxidants &amp; Redox Signaling (2007), 9(11), 1825-1836

CODEN: ARSIF2; ISSN: 1523-0864

PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mitochondria-targeted drug mitoquinone (MitoQ) has been used as an antioxidant that may selectively block mitochondrial oxidative damage; however, it has been recently suggested to increase reactive oxygen species (ROS) generation in malate- and glutamate-fueled mitochondria. To address this controversy, we studied the effects of MitoQ on endothelial and mitochondrial ROS production. We found that in a cell-free system with flavin-containing enzyme cytochrome P 450 reductase, MitoQ is a very efficient redox cycling agent and produced more superoxide compared with equal concns. of menadione (10-1000 nM). Treatment of endothelial cells with MitoQ resulted in a dramatic increase in superoxide production. In isolated mitochondria, MitoQ increased complex I-driven mitochondrial ROS production, whereas supplementation with ubiquinone-10 had no effect on ROS production. Similar results were observed in mitochondria isolated from endothelial cells incubated for 1 h with MitoQ. Inhibitor anal. suggested that the redox cycling of MitoQ occurred at two sites on complex I, proximal and distal to the rotenone-binding site. This was confirmed by demonstrating the redox cycling of MitoQ on purified mitochondrial complex I as well as NADH-fueled submitochondrial particles. Mitoquinone time- and dose-dependently increased endothelial cell apoptosis. These findings demonstrate that MitoQ may be prooxidant and proapoptotic because its quinone group can participate in redox cycling and superoxide production. In light of these results, studies using mitoquinone as an antioxidant should be interpreted with caution.

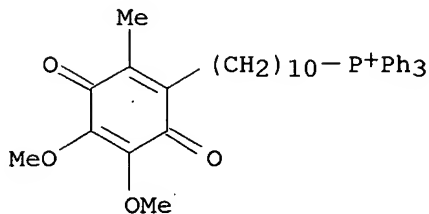
IT 845959-50-4

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(mitochondrial redox cycling of mitoquinone leads to superoxide production and cellular apoptosis)

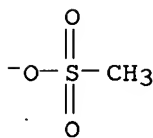
RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 444890-41-9  
CMF C37 H44 O4 P

CM 2

CRN 16053-58-0  
CMF C H3 O3 S

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:1030540 CAPLUS

DOCUMENT NUMBER: 147:481558

TITLE: Mitochondrial uncouplers with an extraordinary dynamic range

AUTHOR(S): Lou, Phing-How; Hansen, Birgit S.; Olsen, Preben H.; Tullin, Soren; Murphy, Michael P.; Brand, Martin D.

CORPORATE SOURCE: MRC Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK

SOURCE: Biochemical Journal (2007), 407(1), 129-140

CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have discovered that some weak uncouplers (typified by butylated hydroxytoluene) have a dynamic range of more than 10<sup>6</sup> in vitro: the concentration

giving measurable uncoupling is less than one millionth of the concentration causing full uncoupling. They achieve this through a high-affinity interaction with the mitochondrial adenine nucleotide translocase that causes significant but limited uncoupling at extremely low uncoupler concns., together with more conventional uncoupling at much higher concns. Uncoupling at the translocase is not by a conventional weak acid/anion cycling mechanism since it is also caused by substituted triphenylphosphonium mols., which are not anionic and cannot protonate.

Covalent attachment of the uncoupler to a mitochondrially targeted hydrophobic cation sensitizes it to membrane potential, giving a small addnl. effect. The wide dynamic range of these uncouplers in isolated mitochondria and intact cells reveals a novel allosteric activation of proton transport through the adenine nucleotide translocase and provides a promising starting point for designing safer uncouplers for obesity therapy.

IT 845959-50-4 845959-58-2 954111-83-2

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(mitochondrial uncouplers with extraordinary dynamic range)

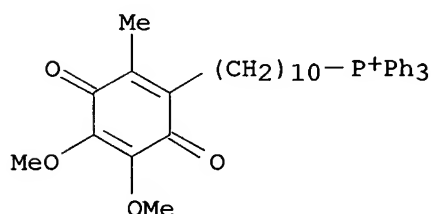
RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 444890-41-9

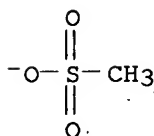
CMF C37 H44 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



RN 845959-58-2 CAPLUS

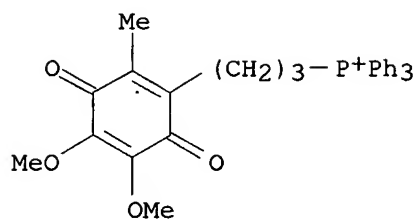
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 794485-93-1

CMF C30 H30 O4 P

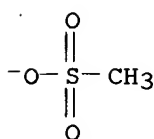




CM 2

CRN 16053-58-0

CMF C H3 O3 S



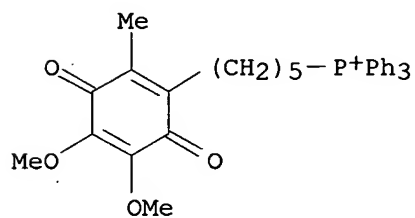
RN 954111-83-2 CAPLUS

CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 794485-94-2

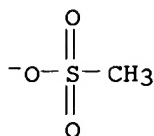
CMF C32 H34 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:965666 CAPLUS

DOCUMENT NUMBER: 148:135860

TITLE: Mitochondria-targeted antioxidants do not prevent tumor necrosis factor-induced necrosis of L929 cells

AUTHOR(S): Jarvis, Reagan M.; Goettert, Jana; Murphy, Michael P.; Ledgerwood, Elizabeth C.

CORPORATE SOURCE: Department of Biochemistry, University of Otago, Dunedin, N. Z.

SOURCE: Free Radical Research (2007), 41(9), 1041-1046

CODEN: FRARER; ISSN: 1071-5762

PUBLISHER: Informa Healthcare

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mitochondrial production of reactive oxygen species (ROS) is widely reported as a central effector during TNF-induced necrosis. The effect of a family of mitochondria-targeted antioxidants on TNF-induced necrosis of L929 cells was studied. While the commonly used lipid-soluble antioxidant BHA effectively protected cells from TNF-induced necrosis, the mitochondria-targeted antioxidants MitoQ3, MitoQ5, MitoQ10 and MitoPBN had no effect on TNF-induced necrosis. Since BHA also acts as an uncoupler of mitochondrial membrane potential, two addnl. uncouplers were tested. FCCP and CCCP both provided dose-dependent inhibition of TNF-induced necrosis. In conclusion, the generation of mitochondrial ROS may not be necessary for TNF-induced necrosis. Instead, these results suggest alternative mitochondrial functions, such as a respiration-dependent process, are critical for necrotic death.

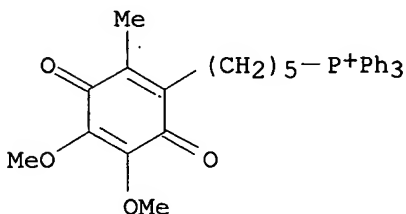
IT 764723-90-2 845959-57-1

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitochondria-targeted antioxidants do not prevent tumor necrosis factor-induced necrosis of L929 cells)

RN 764723-90-2 CAPLUS

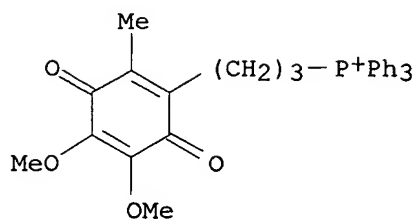
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



● I<sup>-</sup>

RN 845959-57-1 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:922908 CAPLUS

DOCUMENT NUMBER: 147:356077

TITLE: Targeting antioxidants to mitochondria and cardiovascular diseases: the effects of mitoquinone

AUTHOR(S): Rocha, Milagros; Victor, Victor Manuel

CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, Universitat de Valencia, Valencia, Spain

SOURCE: Medical Science Monitor (2007), 13(7), RA132-RA145  
CODEN: MSMOFR; ISSN: 1234-1010

PUBLISHER: International Scientific Literature, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Mitochondria have long been known to play a critical role in maintaining the bioenergetic status of cells under physiol. conditions. Mitochondria produce large amts. of free radicals, and mitochondrial oxidative damage can contribute to a range of degenerative conditions including cardiovascular diseases (CVDs). Although the mol. mechanisms responsible for mitochondrion-mediated disease processes are not correctly understood, oxidative stress seems to play an important role. Consequently, the selective inhibition of mitochondrial oxidative damage is an obvious therapeutic strategy. This review considers the process of CVD from a mitochondrial perspective and provides a summary of the following areas: reactive oxygen species (ROS) production and its role in pathophysiol. processes such as CVD, currently available antioxidants and possible reasons for their efficacy and inefficacy in ameliorating oxidative stress-mediated diseases, and recent developments in mitochondria-targeted antioxidants that concentrate on the matrix-facing surface

of the inner mitochondrial membrane. These mitochondrion-targeted antioxidants have been developed by conjugating the lipophilic triphenylphosphonium cation to antioxidant moieties such as ubiquinol. These compds. pass easily through biol. membranes and, due to their pos. charge, they accumulate several-hundred-fold within mitochondria. In this way they protect against mitochondrial oxidative damage and show potential as a future therapy for CVDs.

IT 845959-50-4, Mitoquinone

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(loss of control of reactive oxygen species formation in mitochondria leads to pathol. of cardiovascular disease in animals and mitoquinone protect against mitochondrial oxidative damage and showed potential as future therapy for CVD)

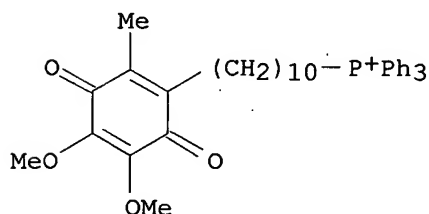
RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 444890-41-9

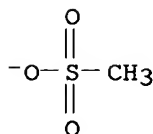
CMF C37 H44 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



REFERENCE COUNT: 126 THERE ARE 126 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:818711 CAPLUS

DOCUMENT NUMBER: 147:335184

TITLE: Drug evaluation: MitoQ - a mitochondrial-targeted antioxidant

AUTHOR(S): Tauskela, Joseph S.

CORPORATE SOURCE: Institute for Biological Sciences, Synaptic Pathophysiology Group, National Research Council, Ottawa, ON, K1A 0R6, Can.

SOURCE: IDrugs (2007), 10(6), 399-412  
CODEN: IDRUFN; ISSN: 1369-7056

PUBLISHER: Thomson Scientific

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. MitoQ is an orally active antioxidant that has the ability to target mitochondrial dysfunction. The agent is currently under

development by Antipodean Pharmaceuticals Inc and is in phase II clin. trials for Parkinson's disease and liver damage associated with HCV infection. MitoQ demonstrated encouraging preclin. results in numerous studies in isolated mitochondria, cells and tissues undergoing oxidative stress and apoptotic death. The aim of MitoQ is to not only mimic the role of the endogenous mitochondrial antioxidant coenzyme Q10 (CoQ10), but also to substantially augment the antioxidant capacity of the coenzyme to supraphysiol. levels in a mitochondrial membrane potential-dependent manner. MitoQ represents the first foray into the clinic of an attempt to deliver an antioxidant to an intracellular region that is responsible for the formation of increased levels of potentially deleterious reactive oxygen species. Results from the clin. trials with MitoQ will have important repercussions regarding the relevance of a mitochondria-targeted approach.

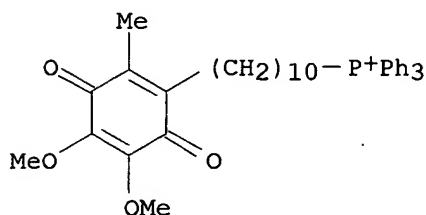
IT 444890-41-9, MitoQ

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitochondrial-targeted antioxidant MitoQ)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT:

91

THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:739270 CAPLUS

DOCUMENT NUMBER: 147:273456

TITLE: Quantitation and metabolism of mitoquinone, a mitochondria-targeted antioxidant, in rat by liquid chromatography/tandem mass spectrometry

AUTHOR(S): Li, Yan; Zhang, Hu; Fawcett, J. Paul; Tucker, Ian G.

CORPORATE SOURCE: School of Pharmacy, University of Otago, Dunedin, N. Z.

SOURCE: Rapid Communications in Mass Spectrometry (2007), 21(13), 1958-1964

CODEN: RCMSEF; ISSN: 0951-4198

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mitoquinone (MitoQ10 mesylate) is a mitochondria-targeted antioxidant undergoing development for the treatment of neurodegenerative diseases. The aim of this study was to develop and validate an assay based on liquid chromatog./tandem mass spectrometry (LC/MS/MS) to determine mitoquinone and to detect and identify the metabolites of MitoQ10 in rat plasma after an oral dose. After a simple protein precipitation step, plasma samples were analyzed by

reversed-phase liquid chromatog. using gradient elution with acetonitrile/water/formic acid. Electrospray ionization in the pos. ion mode with multiple reaction monitoring (MRM) was used to analyze mitoquinone employing the deuterated compound (d3-MitoQ10 mesylate) as internal standard. The calibration curve for mitoquinone was linear over the concentration range 0.5-250 ng/mL with a correlation coefficient >0.995. The method

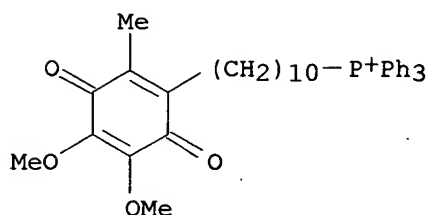
was sensitive (limit of quantitation 0.5 ng/mL) and had acceptable accuracy (relative error <8.7%) and precision (intra- and inter-day coefficient of variation <12.4%). Recoveries of mitoquinone at concns. of 1.5, 20 and 200 ng/mL were in the range 87-114%. The method was successfully applied to a pharmacokinetic study in rat after a single oral dose in which four metabolites of MitoQ10 were tentatively identified as hydroxylated MitoQ10, desmethyl MitoQ10 and the glucuronide and sulfate conjugates of the quinol form of MitoQ10.

IT 444890-41-9

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(quantitation and metabolism of mitochondria-targeted antioxidant mitoquinone in rat)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT:

9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:542355 CAPLUS

DOCUMENT NUMBER: 147:157119

TITLE: Targeting antioxidants to mitochondria: a potential new therapeutic strategy for cardiovascular diseases

AUTHOR(S): Victor, V. M.; Rocha, M.

CORPORATE SOURCE: Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, 28029, Spain

SOURCE: Current Pharmaceutical Design (2007), 13(8), 845-863  
CODEN: CPDEFP; ISSN: 1381-6128

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Mitochondria produce large amts. of free radicals and play an important role in the life and death of a cell. Thus, mitochondrial oxidative damage and dysfunction contribute to a number of cell pathologies that manifest themselves through a range of conditions including ischemia-reperfusion injury, sepsis, diabetes, atherosclerosis and, consequently, cardiovascular diseases (CVD). In fact, endothelial dysfunction, characterized by a loss of nitric oxide (NO) bioactivity, occurs early on in the development of atherosclerosis, and dets. future

vascular complications. Although the mol. mechanisms responsible for mitochondria-mediated disease processes are not yet clear, oxidative stress seems to play an important role. This review considers the process of CVD from a mitochondrial perspective. Accordingly, strategies for the targeted delivery of antioxidants to mitochondria are being developed. In this review, we will provide a summary of the following areas: the cellular metabolism of reactive oxygen species (ROS) and its role in pathophysiol. processes such as CVD; currently available antioxidants and possible reasons for their efficacy and inefficacy in ameliorating oxidative stress-mediated diseases; recent developments in mitochondrially-targeted antioxidants that concentrate on the matrix-facing surface of the inner mitochondrial membrane and therefore protect against mitochondrial oxidative damage, and their therapeutic potential for future treatment of CVDs. More pre-clin. and clin. studies, however, are necessary in order to evaluate the effectiveness and toxicity of mitochondrially-targeted antioxidants.

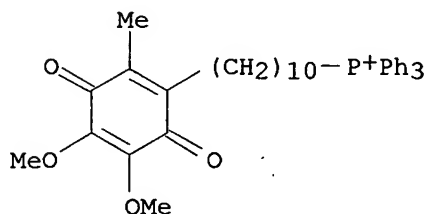
IT 444890-41-9, MitoQ

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(targeting antioxidants to mitochondria with a potential new therapeutic strategy for cardiovascular diseases)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 156 THERE ARE 156 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:522753 CAPLUS

DOCUMENT NUMBER: 147:202729

TITLE: Mitochondrial targeting of quinones: Therapeutic implications

AUTHOR(S): Cocheme, Helena M.; Kelso, Geoffrey F.; James, Andrew M.; Ross, Meredith F.; Trnka, Jan; Mahendiran, Thabo; Asin-Cayuela, Jordi; Blaikie, Frances H.; Manas, Abdul-Rahman B.; Porteous, Carolyn M.; Adlam, Victoria J.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: MRC Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK

SOURCE: Mitochondrion (2007), 7(Suppl.), S94-S102

CODEN: MITOCN; ISSN: 1567-7249

PUBLISHER: Elsevier B.V.

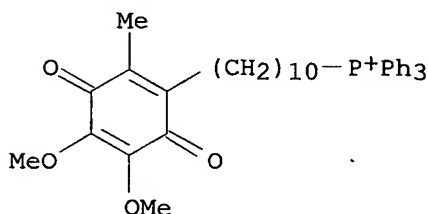
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Mitochondrial oxidative damage contributes to a range of degenerative diseases. Ubiquinones have been shown to protect

mitochondria from oxidative damage, but only a small proportion of externally administered ubiquinone is taken up by mitochondria. Conjugation of the lipophilic triphenylphosphonium cation to a ubiquinone moiety has produced a compound, MitoQ, which accumulates selectively into mitochondria. MitoQ passes easily through all biol. membranes and, because of its pos. charge, is accumulated several hundred-fold within mitochondria driven by the mitochondrial membrane potential. MitoQ protects mitochondria against oxidative damage in vitro and following oral delivery, and may therefore form the basis for mitochondria-protective therapies.

IT 444890-41-9, MitoQ  
 RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (mitochondrial targeting of quinones and therapeutic implications)  
 RN 444890-41-9 CAPLUS  
 CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN  
 ACCESSION NUMBER: 2007:513564 CAPLUS  
 DOCUMENT NUMBER: 147:160001  
 TITLE: Interaction of the Mitochondria-targeted Antioxidant MitoQ with Phospholipid Bilayers and Ubiquinone Oxidoreductases  
 AUTHOR(S): James, Andrew M.; Sharpley, Mark S.; Manas, Abdul-Rahman B.; Frerman, Frank E.; Hirst, Judy; Smith, Robin A. J.; Murphy, Michael P.  
 CORPORATE SOURCE: Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK  
 SOURCE: Journal of Biological Chemistry (2007), 282(20), 14708-14718  
 CODEN: JBCHA3; ISSN: 0021-9258  
 PUBLISHER: American Society for Biochemistry and Molecular Biology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB MitoQ10 is a ubiquinone that accumulates within mitochondria driven by a conjugated lipophilic triphenylphosphonium cation (TPP+). Once there, MitoQ10 is reduced to its active ubiquinol form, which has been used to prevent mitochondrial oxidative damage and to infer the involvement of reactive oxygen species in signaling pathways. Here we show MitoQ10 is effectively reduced by complex II, but is a poor substrate for complex I, complex III, and electron-transferring flavoprotein (ETF):quinone oxidoreductase (ETF-QOR). This differential reactivity could be explained



if the bulky TPP+ moiety sterically hindered access of the ubiquinone group to enzyme active sites with a long, narrow access channel. Using a combination of mol. modeling and an uncharged analog of MitoQ10 with similar sterics (tritylQ10), we infer that the interaction of MitoQ10 with complex I and ETF-QOR, but not complex III, is inhibited by its bulky TPP+ moiety. To explain its lack of reactivity with complex III we show that the TPP+ moiety of MitoQ10 is ineffective at quenching pyrene fluorophors deeply buried within phospholipid bilayers and thus is positioned near the membrane surface. This superficial position of the TPP+ moiety, as well as the low solubility of MitoQ10 in non-polar organic solvents, suggests that the

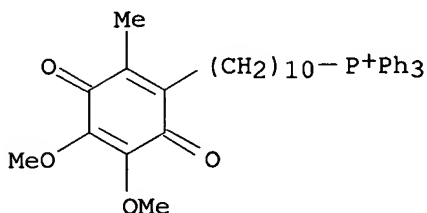
concentration of the entire MitoQ10 mol. in the membrane core is very limited. As overlaying MitoQ10 onto the structure of complex III indicates that MitoQ10 cannot react with complex III without its TPP+ moiety entering the low dielec. of the membrane core, we conclude that the TPP+ moiety does anchor the tethered ubiquinol group out of reach of the active site(s) of complex III, thus explaining its slow oxidation. In contrast the ubiquinone moiety of MitoQ10 is able to quench fluorophors deep within the membrane core, indicating a high concentration of the ubiquinone moiety within the membrane and explaining its good anti-oxidant efficacy. These findings will facilitate the rational design of future mitochondria-targeted mols.

IT 444890-41-9, MitoQ

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(interaction of mitochondria-targeted antioxidant MitoQ with phospholipid bilayers and ubiquinone oxidoreductases)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:407185 CAPLUS

DOCUMENT NUMBER: 147:63256

TITLE: Transport and metabolism of MitoQ10, a mitochondria-targeted antioxidant, in Caco-2 cell monolayers

AUTHOR(S): Li, Yan; Fawcett, J. Paul; Zhang, Hu; Tucker, Ian G.  
CORPORATE SOURCE: School of Pharmacy, University of Otago, Dunedin, N. Z.

SOURCE: Journal of Pharmacy and Pharmacology (2007), 59(4), 503-511

CODEN: JPPMAB; ISSN: 0022-3573

PUBLISHER: Pharmaceutical Press

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 147:63256

AB Mitoquinone (MitoQ10 mesylate) is a mitochondria-targeted antioxidant formulated for oral administration in the treatment of neurodegenerative diseases. We have investigated the absorption and metabolism of MitoQ10 in Caco-2 cell monolayers. The intracellular accumulation of MitoQ10 was 18-41% of the total amount of MitoQ10 added. Some of the intracellular MitoQ10 was reduced to mitoquinol and subsequently metabolized to glucuronide and sulfate conjugates. Transport of MitoQ10 was polarized with the apparent permeability (Papp) from basolateral (BL) to apical (AP) (PappBL→AP) being >2.5-fold the Papp from apical to basolateral (PappAP→BL). In the presence of 4% bovine serum albumin on the basolateral side, the PappAP→BL value increased 7-fold compared with control. The PappBL→AP value decreased by 26%, 31%, and 61% in the presence of verapamil 100 μM, ciclosporin 10 and 30 μM, resp., whereas the PappAP→BL value increased 71% in the presence of ciclosporin 30 μM. Apical efflux of mitoquinol sulfate and mitoquinol glucuronide conjugates was significantly decreased by ciclosporin 30 μM and the breast cancer receptor protein (BCRP) inhibitor, reserpine 25 μM, resp. These results suggested that the bioavailability of MitoQ10 may be limited by intracellular metabolism and the action of P-glycoprotein and BCRP. However, the dramatic increase in absorptive Papp in the presence of bovine serum albumin on the receiver side suggests these barrier functions may be less significant in-vivo.

IT 845959-50-4, Mitoquinone mesylate

RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(transport and metabolism of MitoQ10 as mitochondria-targeted antioxidant, in Caco-2 cell monolayers)

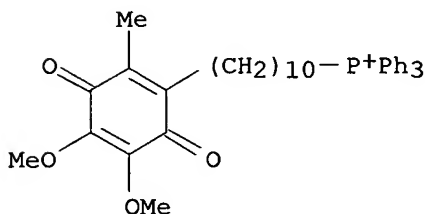
RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 444890-41-9

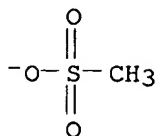
CMF C37 H44 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:70572 CAPLUS

DOCUMENT NUMBER: 146:182912

TITLE: High Concentration of Antioxidants N-Acetylcysteine and Mitoquinone-Q Induces Inter cellular Adhesion Molecule 1 and Oxidative Stress by Increasing Intracellular Glutathione

AUTHOR(S): Mukherjee, Tapan K.; Mishra, Anurag K.; Mukhopadhyay, Srirupa; Hoidal, John R.

CORPORATE SOURCE: Department of Internal Medicine, Pulmonary Division, University of Utah Health Science Center, Salt Lake City, UT, 84112, USA

SOURCE: Journal of Immunology (2007), 178(3), 1835-1844  
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

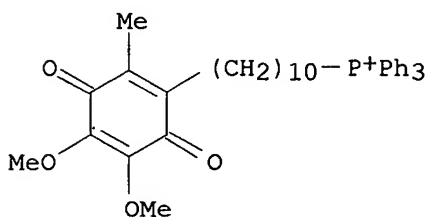
AB In endothelial cells, the intracellular level of glutathione is depleted during offering protection against proinflammatory cytokine TNF- $\alpha$ -induced oxidative stress. Administration of anti-inflammatory drugs, i.e., N-acetylcysteine (NAC) or mitoquinone-Q (mito-Q) in low concns. in the human pulmonary aortic endothelial cells offered protection against depletion of reduced glutathione and oxidative stress mediated by TNF- $\alpha$ . However, this study addressed that administration of NAC or mito-Q in high concns. resulted in a biphasic response by initiating an enhanced generation of both reduced glutathione and oxidized glutathione and enhanced production of reactive oxygen species, along with carbonylation and glutathionylation of the cellular proteins. This study further addressed that I $\kappa$ B kinase (IKK), a phosphorylation-dependent regulator of NF- $\kappa$ B, plays an important regulatory role in the TNF- $\alpha$ -mediated induction of the inflammatory cell surface mol. ICAM-1. Of the two catalytic subunits of IKK (IKK $\alpha$  and IKK $\beta$ ), low concns. of NAC and mito-Q activated IKK $\alpha$  activity, thereby inhibiting the downstream NF- $\kappa$ B and ICAM-1 induction by TNF- $\alpha$ . High concns. of NAC and mito-Q instead caused glutathionylation of IKK $\alpha$ , thereby inhibiting its activity that in turn enhanced the downstream NF- $\kappa$ B activation and ICAM-1 expression by TNF- $\alpha$ . Thus, establishing IKK $\alpha$  as an anti-inflammatory mol. in endothelial cells is another focus of this study. This is the first report that describes a stressful situation in the endothelial cells created by excess of antioxidative and anti-inflammatory agents NAC and mito-Q, resulting in the generation of reactive oxygen species, carbonylation and glutathionylation of cellular proteins, inhibition of IKK $\alpha$  activity, and up-regulation of ICAM-1 expression.

IT 444890-41-9, MitoQ

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(high concentration of antioxidants N-acetylcysteine and mitoquinone-Q induces

ICAM-1 and oxidative stress by increasing intracellular glutathione)  
 RN 444890-41-9 CAPLUS  
 CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 19 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1348478 CAPLUS

DOCUMENT NUMBER: 146:178916

TITLE: Reactive Oxygen and Targeted Antioxidant Administration in Endothelial Cell Mitochondria  
 AUTHOR(S): O'Malley, Yunxia; Fink, Brian D.; Ross, Nicolette C.; Prisinzano, Thomas E.; Sivitz, William I.

CORPORATE SOURCE: Iowa City Veterans Affairs Medical Center, Department of Internal Medicine, Division of Endocrinology and Metabolism and the College of Pharmacy, Division of Medicinal and Natural Products Chemistry, University of Iowa, Iowa City, IA, 52242, USA

SOURCE: Journal of Biological Chemistry (2006), 281(52), 39766-39775

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We used fluorescent probes and EPR to study the mechanism(s) underlying reactive oxygen species (ROS) production by endothelial cell mitochondria and the action of mitoquinol (MitoQ), a mitochondria-targeted antioxidant. ROS measured by fluorescence resulted from complex I superoxide released to the matrix and converted to H<sub>2</sub>O<sub>2</sub>. In contrast, EPR largely detected superoxide generated at complex III and effluxed outward. ROS fluorescence by mitochondria fueled by the complex II substrate, succinate, was substantial but markedly inhibited by rotenone. Superoxide, detected by EPR, in succinate-fueled mitochondria was not inhibited by rotenone and likely derived from semiquinone formation at complex III. Mitoquinol decreased H<sub>2</sub>O<sub>2</sub> fluorescence by succinate-fueled mitochondria but had little effect on the EPR signal for superoxide. This was not associated with a detectable decrease in membrane potential. Mitoquinol markedly enhanced ROS fluorescence in mitochondria fueled by the complex I substrates, glutamate and malate. Inhibitor studies suggested that this occurred in complex I, at one or more Q binding pockets. The above effects of mitoquinol were determined in mitochondria isolated and subsequently exposed to the targeted antioxidant. However, similar effects were observed in mitochondria after antecedent exposure to mitoquinol/mitoquinone in culture, suggesting that the agent is retained

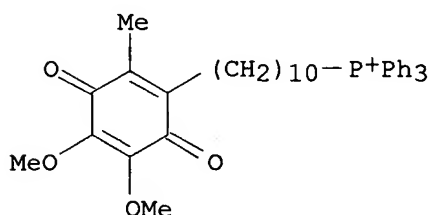
after isolation of the organelles. In conclusion, ROS production in bovine aortic endothelial cell mitochondria results largely from reverse transport to complex I and through the Q cycle in complex III. Mitoquinol blocks ROS from reverse electron transport but increases superoxide production derived from forward transport. These effects likely occur at one or more Q binding sites in complex I.

IT 444890-41-9, MitoQ

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(MitoQ acts in complex I to block ROS generated by reverse electron transport but increases superoxide production associated with forward electron transport)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1112822 CAPLUS

DOCUMENT NUMBER: 145:495544

TITLE: Antitumor sustained-release injection containing taxane and its synergistic agent

INVENTOR(S): Liu, Yuyan

PATENT ASSIGNEE(S): Jinan Kangquan Pharmaceutical Science and Technology Co., Ltd., Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 34pp.  
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1846689	A	20061018	CN 2006-10200114	20060210
PRIORITY APPLN. INFO.:			CN 2006-10200114	20060210

AB The patent antitumor sustained-release injection is comprised of (A) sustained-release microsphere comprising antitumor effective constituent 0.5-60%, sustained-release adjuvant 40-99% and suspending agent 0.0-30.0%; and (B) solvent. The antitumor effective constituent is taxane and/or the taxane synergistic agent which is selected from antimitotic drugs, alkylating agents and/or antimetabolite agents. The taxane is selected from taxol, docetaxel, paclitaxel-2'-hydroxy, 10-deacetylbaaccatin III, and 7-epi-taxol. The antimitotic drug is selected from one of podophyllotoxin, mitonafide, mitotane, colchicine, colchisal, naphthol,

cytochalasin, etc., or the mixture thereof. The alkylating agent is selected from one of cyclophosphamide, melphalan, chlorambucil, ifosfamide, etc., or the mixture thereof. The antimetabolite agent is selected from one of 6-mercaptopurine, 5-fluorouracil, alimta, alimta disodium, etc., or the mixture thereof. The sustained-release adjuvant is selected from one of (a) polylactic acid; (b) Polyglycolic acid-hydroxy acetic acid copolymer; (c) polifeprosan; (d) ethene-vinyl acetate copolymer; (e) difatty acid-sebacic acid copolymer; (f) poly(erucic acid dimer-sebacic acid) copolymer; (g) poly(fumaric acid-sebacic acid) copolymer; and (h) xylitol, oligosaccharide, chondroitin, chitin, hyaluronic acid, collagens, gelatin, etc.; or the mixture thereof. The suspending agent is one of (a) 0.5-3.0 % (sodium) CM-cellulose; (b) 5-15 % mannitol; (c) 5-15 % sorbitol; (d) 0.1-1.5 % surfactant; (e) 0.1-0.5 % tween 20; or (f) (iodine) glycerin, dimethicone, propylene glycol, or carbomer; or the mixture thereof. Said sustained-release preparation can reduce toxic reaction, at the same time can increase selectively drug concentration, and enhance therapeutic effectiveness.

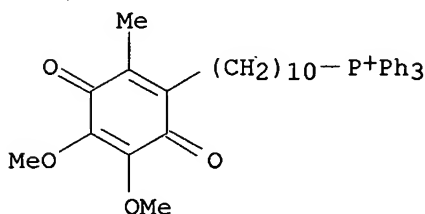
IT 444890-41-9, Mito-Q

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antitumor sustained-release injection containing taxane and its synergistic agent)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



L3 ANSWER 21 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1067714 CAPLUS

DOCUMENT NUMBER: 145:419306

TITLE: Preparation of mitoquinone derivatives as mitochondrially targeted antioxidants

INVENTOR(S): Taylor, Kenneth Martin; Smith, Robin A. J.

PATENT ASSIGNEE(S): Antipodean Pharmaceuticals, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 57pp., Cont.-in-part of U.S. Ser. No. 172,916.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

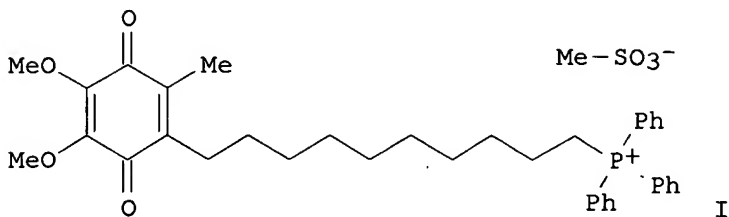
FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060229278	A1	20061012	US 2006-355518	20060215

WO 9926954 A1 19990603 WO 1998-NZ173 19981125  
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW  
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
US 6331532 B1 20011218 US 2000-577877 20000525  
US 20020052342 A1 20020502 US 2001-968838 20011003  
US 20030069208 A1 20030410 US 2002-272914 20021018  
AU 2003204144 A1 20030612 AU 2003-204144 20030512  
AU 2003204144 B2 20070301  
US 20040106579 A1 20040603 US 2003-722542 20031128  
WO 2005019232 A1 20050303 WO 2004-NZ196 20040823  
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
US 20050245487 A1 20051103 US 2005-172916 20050705  
US 7232809 B2 20070619  
US 20070270381 A1 20071122 US 2007-799779 20070502  
PRIORITY APPLN. INFO.: WO 1998-NZ173 A2 19981125  
US 2000-577877 A1 20000525  
US 2001-968838 B1 20011003  
US 2002-272914 B1 20021018  
NZ 2003-527800 A 20030822  
NZ 2003-529153 A 20031023  
US 2003-722542 B1 20031128  
NZ 2004-533556 A 20040614  
WO 2004-NZ196 A1 20040823  
US 2005-172916 A2 20050705  
NZ 1997-329255 A 19971125  
AU 1999-16965 A3 19981125  
NZ 1998-329255 A 19981125

OTHER SOURCE(S): MARPAT 145:419306  
GI



AB This invention relates to pharmaceutically acceptable amphiphilic antioxidant compds., compns. and dosage forms comprising the compds. The compds., compns., dosage forms, uses and methods are useful in the treatment of diseases or conditions associated with oxidative stress. Thus, I 1:2 complex  $\beta$ -cyclodextrin with was prepared, and tested for stability and pharmacokinetics.

IT 845959-56-0P  
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)

RN 845959-56-0 CAPLUS

CN  $\beta$ -Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (2:1) (9CI)  
 (CA INDEX NAME)

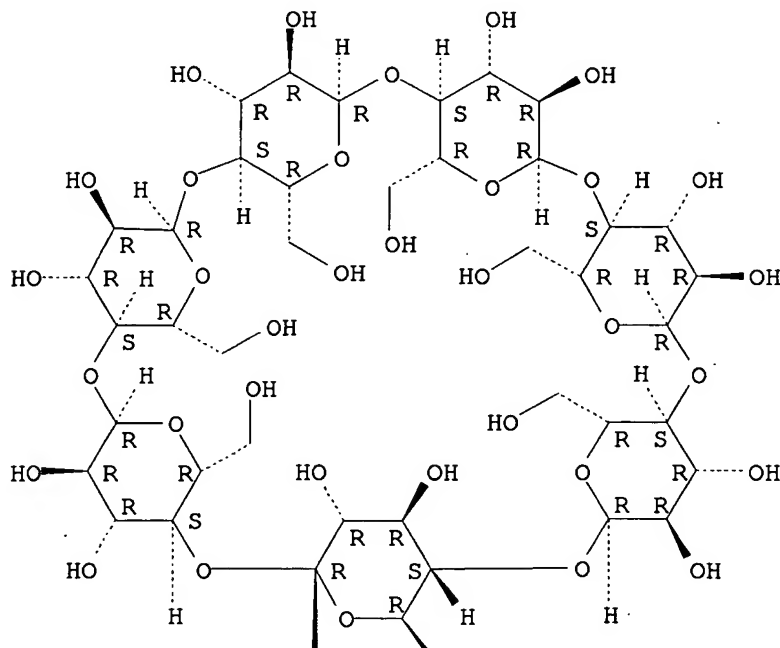
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CRN 7585-39-9

CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A





PAGE 2-A



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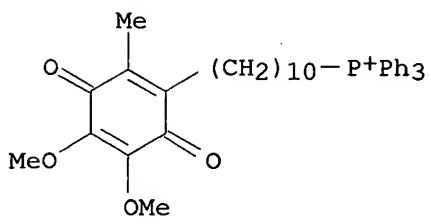
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CM 3

CRN 444890-41-9

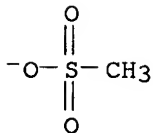
CMF C37 H44 O4 P



CM 4

CRN 16053-58-0

CMF C H3 O3 S



IT 845959-52-6P 911841-84-4P

RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)

RN 845959-52-6 CAPLUS

CN  $\beta$ -Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (1:1) (9CI)  
(CA INDEX NAME)

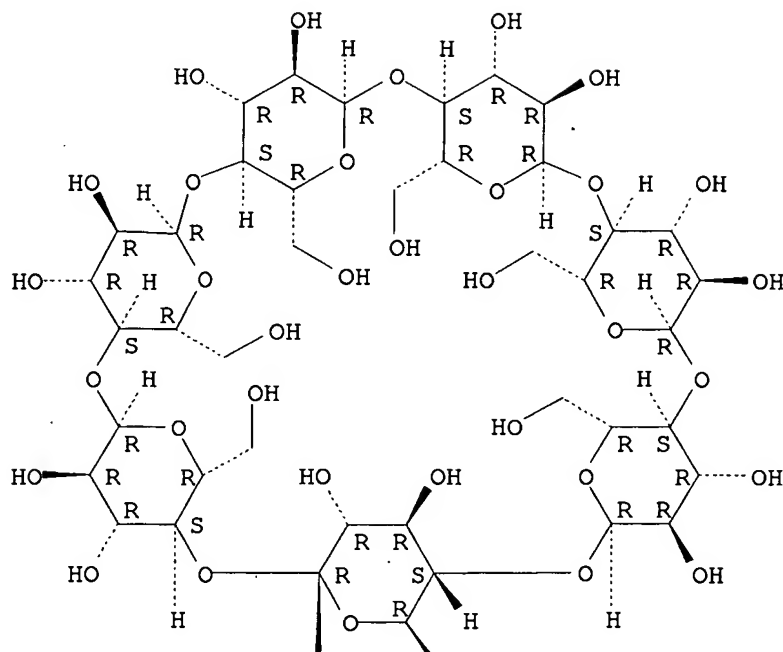
CM 1

CRN 7585-39-9

CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



CM 2

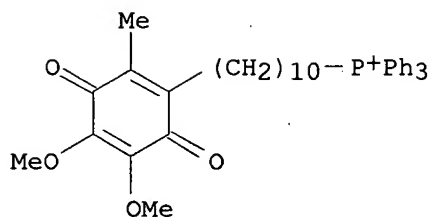
CRN 845959-50-4

CMF C37 H44 O4 P.. C H3 O3 S

CM 3

CRN 444890-41-9

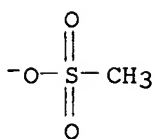
CMF C37 H44 O4 P



CM 4

CRN 16053-58-0

CMF C H3 O3 S



RN 911841-84-4 CAPLUS

CN  $\beta$ -Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (4:1) (9CI)  
(CA INDEX NAME)

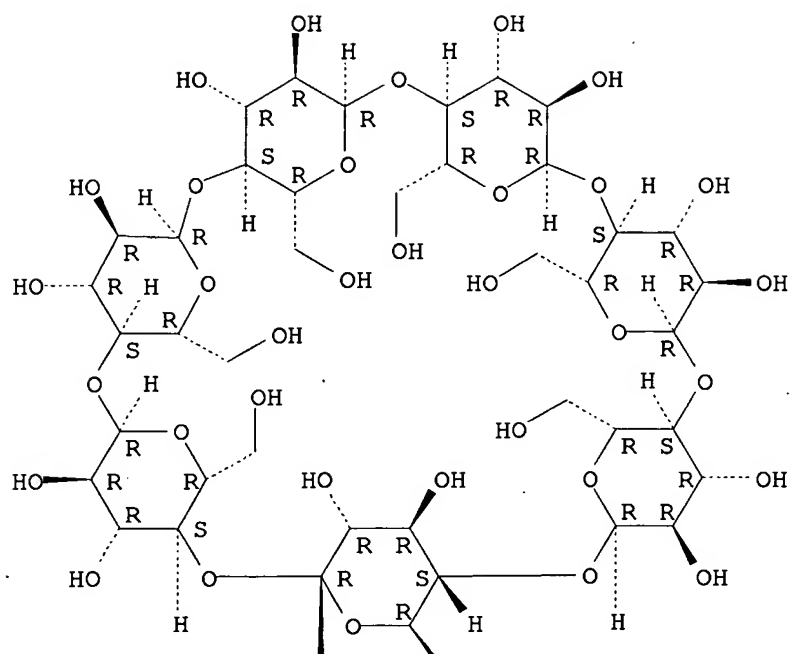
CM 1

CRN 7585-39-9

CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



CM 2

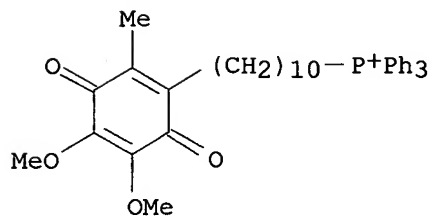
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CMF C37 H44 O4 P . C H3 O3 S

CM 3

CRN 444890-41-9

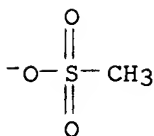
CMF C37 H44 O4 P



CM 4

CRN 16053-58-0

CMF C H3 O3 S



IT 845959-50-4P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)

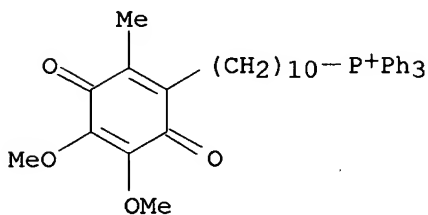
RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 444890-41-9

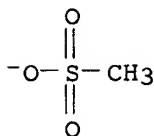
CMF C37 H44 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



IT 764723-90-2P 764723-92-4P 845959-58-2P

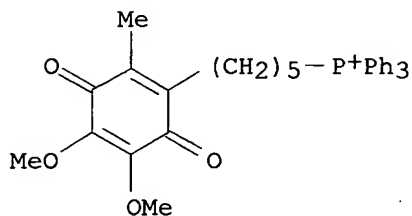
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

## (Uses)

(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)

RN 764723-90-2 CAPLUS

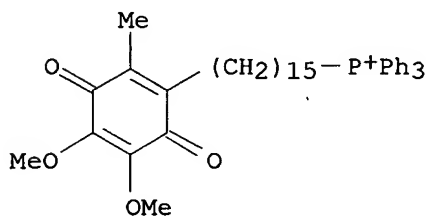
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



● I<sup>-</sup>

RN 764723-92-4 CAPLUS

CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

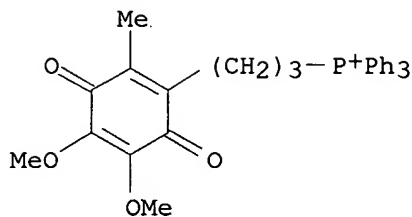
RN 845959-58-2 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 794485-93-1

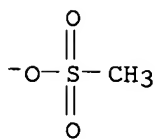
CMF C30 H30 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



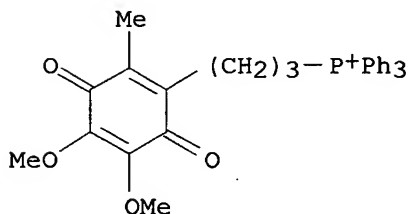
IT 845959-57-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)

RN 845959-57-1 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

● Br<sup>-</sup>

L3 ANSWER 22 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:202663 CAPLUS

DOCUMENT NUMBER: 145:202743

TITLE: The effects of exogenous antioxidants on lifespan and oxidative stress resistance in *Drosophila melanogaster*

AUTHOR(S): Magwere, Tapiwanashe; West, Melanie; Riyahi, Kumars; Murphy, Michael P.; Smith, Robin A. J.; Partridge, Linda

CORPORATE SOURCE: Centre for Research on Aging, Department of Biology,  
University College London, London, WC1E 6BT, UK  
SOURCE: Mechanisms of Ageing and Development (2006), 127(4),  
356-370  
CODEN: MAGDA3; ISSN: 0047-6374  
PUBLISHER: Elsevier Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB We used the fruit fly *Drosophila melanogaster* to test the effects of feeding the superoxide dismutase (SOD) mimetic drugs Euk-8 and -134 and the mitochondria-targeted mitoquinone (MitoQ) on lifespan and oxidative stress resistance of wild type and SOD-deficient flies. Our results reaffirm the findings by other workers that exogenous antioxidant can rescue pathol. associated with compromised defences to oxidative stress, but fail to extend the lifespan of normal, wild type animals. All three drugs showed a dose-dependent increase in toxicity in wild type flies, an effect that was exacerbated in the presence of the redox-cycling drug paraquat. However, important findings from this study were that in SOD-deficient flies, where the antioxidant drugs increased lifespan, the effects were sex-specific and, for either sex, the effects were also variable depending on (1) the stage of development from which the drugs were given, and (2) the magnitude of the dose. These findings place significant constraints on the role of oxidative stress in normal aging.

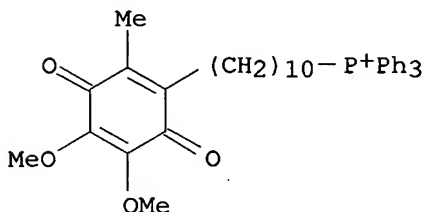
IT 444890-41-9, MitoQ

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antioxidant drug, mitochondria-targeted mitoquinone dose-dependently increased toxicity in wild type flies while it increased lifespan in superoxide dismutase-deficient *Drosophila melanogaster*)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:51133 CAPLUS

DOCUMENT NUMBER: 144:121851

TITLE: Use of mitochondrially targeted antioxidant-lipophilic cation conjugate in the treatment of liver diseases and epithelial cancers.

INVENTOR(S): Froehlich, Eleonore; Kvietikova, Ivica; Zatloukal, Kurt; Schatz, Gottfried; Denk, Helmut; Stumppner, Cornelia; Buck, Charles

PATENT ASSIGNEE(S): Oridis Biomed Forschungs- und Entwicklungs G.m.b.H., Austria



SOURCE: PCT Int. Appl., 61 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006005759	A2	20060119	WO 2005-EP53338	20050712
WO 2006005759	A3	20060511		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005261654	A1	20060119	AU 2005-261654	20050712
CA 2573456	A1	20060119	CA 2005-2573456	20050712
EP 1765413	A2	20070328	EP 2005-775873	20050712
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN 1997403	A	20070711	CN 2005-80023193	20050712
JP 2008506667	T	20080306	JP 2007-520833	20050712
KR 2007030815	A	20070316	KR 2006-725659	20061206
US 20070225255	A1	20070927	US 2007-632149	20070212
PRIORITY APPLN. INFO.:			EP 2004-103318	A 20040713
			WO 2005-EP53338	W 20050712

OTHER SOURCE(S): MARPAT 144:121851

AB The invention discloses the use of a mitochondrially targeted antioxidant, e.g. derivs. of vitamin E, coenzyme Q10 or a glutathione peroxidase mimetic, in the treatment and prevention of liver diseases and/or epithelial cancers. The invention also discloses pharmaceutical compns. containing the antioxidant(s) intended for such use. Furthermore the invention relates to the manufacture of medicaments containing the antioxidant(s)

useful for such prevention and treatment. Compds. of the invention comprise a lipophilic cation covalently coupled to an antioxidant moiety, e.g. (Ph)3P+XR·Z- (X = linking group; R = antioxidant moiety; Z- = anion).

IT 873653-01-1 873653-02-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitochondrially targeted antioxidant-lipophilic cation conjugate for treatment of liver disease and epithelial cancer)

RN 873653-01-1 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide, mixt. with [10-(3,6-dihydroxy-4,5-dimethoxy-2-methylphenyl)decyl]triphenylphosphonium bromide (9CI) (CA INDEX NAME)

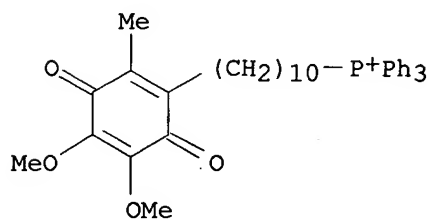
CM 1

10/568,655

07/27/2008

CRN 336184-91-9

CMF C37 H44 O4 P . Br

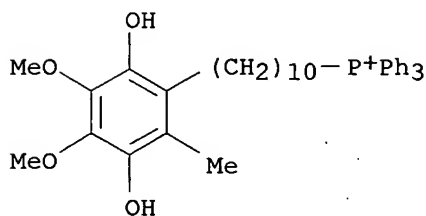


● Br<sup>-</sup>

CM 2

CRN 299975-19-2

CMF C37 H46 O4 P . Br



● Br<sup>-</sup>

RN 873653-02-2 CAPLUS

CN Phosphonium, [10-(3,6-dihydroxy-4,5-dimethoxy-2-methylphenyl)decyl]triphenyl-, methanesulfonate, mixt. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (9CI) (CA INDEX NAME)

CM 1

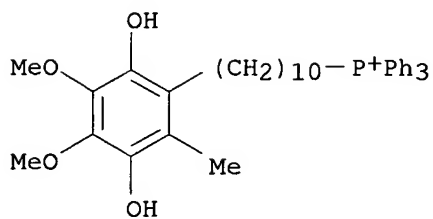
CRN 845959-55-9

CMF C37 H46 O4 P . C H3 O3 S

CM 2

CRN 747398-82-9

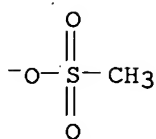
CMF C37 H46 O4 P



CM 3

CRN 16053-58-0

CMF C H3 O3 S



CM 4

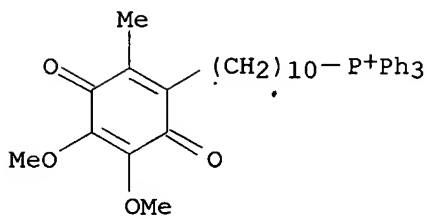
CRN 845959-50-4

CMF C37 H44 O4 P . C H3 O3 S

CM 5

CRN 444890-41-9

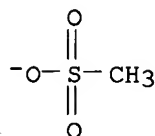
CMF C37 H44 O4 P



CM 6

CRN 16053-58-0

CMF C H3 O3 S



L3 ANSWER 24 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:584282 CAPLUS

DOCUMENT NUMBER: 143:241657

TITLE: Targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury

AUTHOR(S): Adlam, Victoria J.; Harrison, Joanne C.; Porteous, Carolyn M.; James, Andrew M.; Smith, Robin A. J.; Murphy, Michael P.; Sammut, Ivan A.

CORPORATE SOURCE: Department of Chemistry, University of Otago, Dunedin, N. Z.

SOURCE: FASEB Journal (2005), 19(9), 1088-1095

CODEN: FAJOEC; ISSN: 0892-6638

PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mitochondrial oxidative damage contributes to a wide range of pathologies, including cardiovascular disorders and neurodegenerative diseases. Therefore, protecting mitochondria from oxidative damage should be an effective therapeutic strategy. However, conventional antioxidants have limited efficacy due to the difficulty of delivering them to mitochondria in situ. To overcome this problem, we developed mitochondria-targeted antioxidants, typified by MitoQ, which comprises a lipophilic triphenylphosphonium (TPP) cation covalently attached to a ubiquinol antioxidant. Driven by the large mitochondrial membrane potential, the TPP cation concs. MitoQ several hundred-fold within mitochondria, selectively preventing mitochondrial oxidative damage. To test whether MitoQ was active in vivo, we chose a clin. relevant form of mitochondrial oxidative damage: cardiac ischemia-reperfusion injury. Feeding MitoQ to rats significantly decreased heart dysfunction, cell death, and mitochondrial damage after ischemia-reperfusion. This protection was due to the antioxidant activity of MitoQ within mitochondria, as an untargeted antioxidant was ineffective and accumulation of the TPP cation alone gave no protection. Therefore, targeting antioxidants to mitochondria in vivo is a promising new therapeutic strategy in the wide range of human diseases such as Parkinson's disease, diabetes, and Friedreich's ataxia where mitochondrial oxidative damage underlies the pathol.

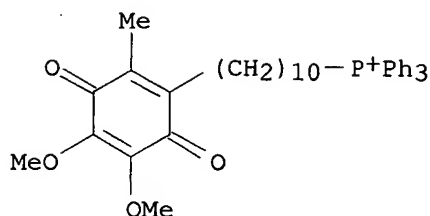
IT 444890-41-9, MitoQ

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:463624 CAPLUS

DOCUMENT NUMBER: 143:148390

TITLE: Interactions of Mitochondria-targeted and Untargeted Ubiquinones with the Mitochondrial Respiratory Chain and Reactive Oxygen Species: implications for the use of exogenous ubiquinones as therapies and experimental tools

AUTHOR(S): James, Andrew M.; Cocheme, Helena M.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK

SOURCE: Journal of Biological Chemistry (2005), 280(22), 21295-21312

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Antioxidants, such as ubiquinones, are widely used in mitochondrial studies as both potential therapies and useful research tools. However, the effects of exogenous ubiquinones can be difficult to interpret because they can also be pro-oxidants or electron carriers that facilitate respiration. Recently we developed a mitochondria-targeted ubiquinone (MitoQ10) that accumulates within mitochondria. MitoQ10 has been used to prevent mitochondrial oxidative damage and to infer the involvement of mitochondrial reactive oxygen species in signaling pathways. However, uncertainties remain about the mitochondrial reduction of MitoQ10, its oxidation by the respiratory chain, and its pro-oxidant potential. Therefore, we compared MitoQ analogs of varying alkyl chain lengths (MitoQn, n = 3-15) with untargeted exogenous ubiquinones. We found that MitoQ10 could not restore respiration in ubiquinone-deficient mitochondria because oxidation of MitoQ analogs by complex III was minimal. Complex II and glycerol 3-phosphate dehydrogenase reduced MitoQ analogs, and the rate depended on chain length. Because of its rapid reduction and negligible oxidation, MitoQ10 is a more effective antioxidant against lipid peroxidn., peroxynitrite and superoxide. Paradoxically, exogenous ubiquinol also autoxidize to generate superoxide, but this requires their deprotonation in the aqueous phase. Consequently, in the presence of phospholipid bilayers, the rate of autoxidn. is proportional to ubiquinol hydrophilicity. Superoxide production by MitoQ10 was insufficient to damage aconitase but did lead to hydrogen peroxide production and nitric oxide consumption, both of which may affect cell signaling pathways. Our results comprehensively describe the

interaction of exogenous ubiquinones with mitochondria and have implications for their rational design and use as therapies and as research tools to probe mitochondrial function.

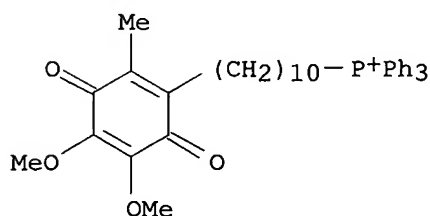
IT 444890-41-9 794485-93-1 794485-94-2  
794485-95-3

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(interactions of mitochondria-targeted and untargeted ubiquinones with the mitochondrial respiratory chain and reactive oxygen species)

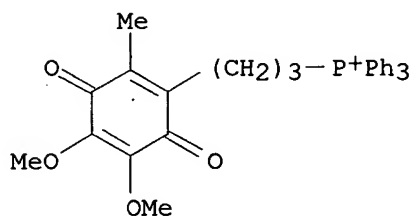
RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



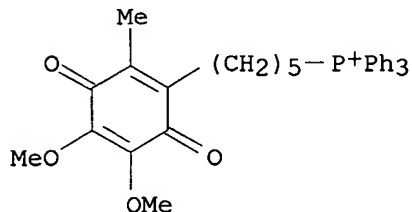
RN 794485-93-1 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl- (CA INDEX NAME)



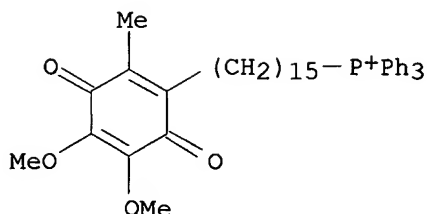
RN 794485-94-2 CAPLUS

CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl- (CA INDEX NAME)



RN 794485-95-3 CAPLUS

CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:182678 CAPLUS

DOCUMENT NUMBER: 142:254662

TITLE: Mitoquinone derivatives used as mitochondrially targeted antioxidants, and preparation thereof

INVENTOR(S): Murphy, Michael Patrick; Smith, Robin

PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.

SOURCE: PCT Int. Appl., 102 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005019233	A1	20050303	WO 2004-NZ197	20040823
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003204144	A1	20030612	AU 2003-204144	20030512
AU 2003204144	B2	20070301		
US 20070238709	A1	20071011	US 2007-568654	20070222
PRIORITY APPLN. INFO.:			NZ 2003-527800	A 20030822
			NZ 2003-529153	A 20031023
			NZ 2004-533555	A 20040614
			AU 1999-16965	A3 19981125
			NZ 1998-329255	A 19981125
			WO 2004-NZ197	W 20040823

OTHER SOURCE(S): CASREACT 142:254662; MARPAT 142:254662

AB This invention discloses methods to screen for, identify, select, and synthesize amphiphilic mitochondrially targeted antioxidant compds., and compns., dosage forms, and methods reliant on these compds. The compds. are all mitoquinone derivs., being methoxyphenyl alkyl triphenylphosphonium or methoxy dioxocyclohexadiene alkyl triphenylphosphonium derivs. The compds., compns., dosage forms and

methods are useful in e.g. the treatment of diseases or conditions associated with oxidative stress.

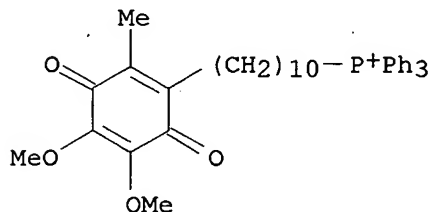
IT 444890-41-9 794485-93-1 794485-94-2

RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

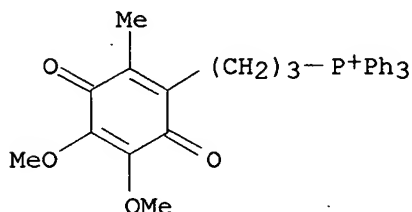
RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



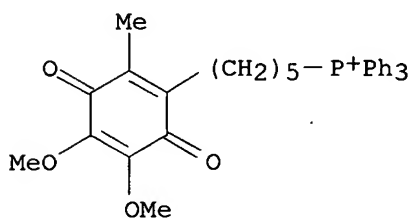
RN 794485-93-1 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl- (CA INDEX NAME)



RN 794485-94-2 CAPLUS

CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl- (CA INDEX NAME)



IT 845959-57-1P

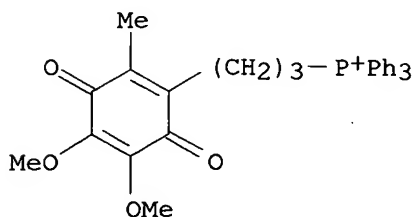
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)



RN 845959-57-1 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

● Br<sup>-</sup>

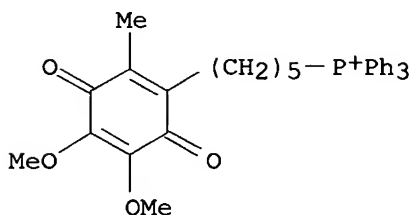
IT 764723-90-2P 764723-92-4P 845959-58-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

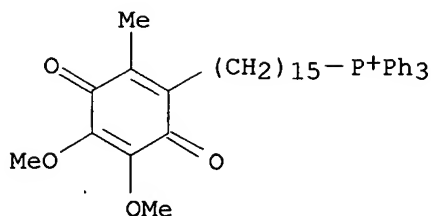
RN 764723-90-2 CAPLUS

CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)

● I<sup>-</sup>

RN 764723-92-4 CAPLUS

CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

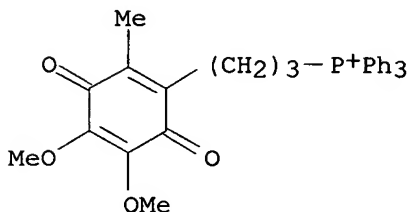
RN 845959-58-2 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 794485-93-1

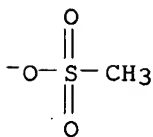
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CM 2

CRN 16053-58-0

CMF C H3 O3 S



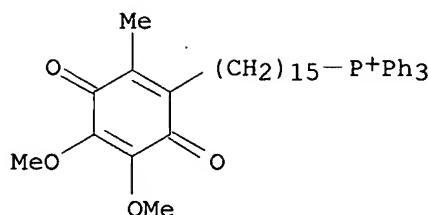
IT 794485-95-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 794485-95-3 CAPLUS

CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:182677 CAPLUS

DOCUMENT NUMBER: 142:254661

TITLE: Mitoquinone derivatives used as mitochondrially targeted antioxidants, and preparation thereof

INVENTOR(S): Taylor, Kenneth Martin; Smith, Robin

PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.

SOURCE: PCT Int. Appl., 143 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005019232	A1	20050303	WO 2004-NZ196	20040823
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003204144	A1	20030612	AU 2003-204144	20030512
AU 2003204144	B2	20070301		
AU 2004266988	A1	20050303	AU 2004-266988	20040823
CA 2536546	A1	20050303	CA 2004-2536546	20040823
EP 1664069	A1	20060607	EP 2004-775122	20040823
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1839142	A	20060927	CN 2004-80024155	20040823
BR 2004013742	A	20061024	BR 2004-13742	20040823
JP 2007503387	T	20070222	JP 2006-523805	20040823
US 20060229278	A1	20061012	US 2006-355518	20060215
MX 2006PA02114	A	20061207	MX 2006-PA2114	20060222
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PRIORITY APPLN. INFO.:			NZ 2003-527800	A 20030822
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AU 1999-16965	A3 19981125
NZ 1998-329255	A 19981125
WO 1998-NZ173	A2 19981125
US 2000-577877	A1 20000525
US 2001-968838	B1 20011003
US 2002-272914	B1 20021018
US 2003-722542	B1 20031128
WO 2004-NZ196	W 20040823
US 2005-172916	A2 20050705

OTHER SOURCE(S): CASREACT 142:254661; MARPAT 142:254661

AB The invention discloses pharmaceutically acceptable amphiphilic antioxidant compds., compns., and dosage forms comprising these compds., and methods and uses reliant on these compds. The compds. are all mitochinone derivs., being methoxyphenyl alkyl triphenylphosphonium or methoxy dioxocyclohexadiene alkyl triphenylphosphonium derivs. The compds., compns., dosage forms, uses, and methods are useful in e.g. the treatment of diseases or conditions associated with oxidative stress.

IT 845959-50-4P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(mitochinone derivative preparation for mitochondrially targeted antioxidant)

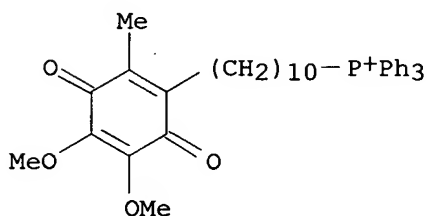
RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 444890-41-9

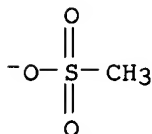
CMF C37 H44 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



IT 845959-59-3P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

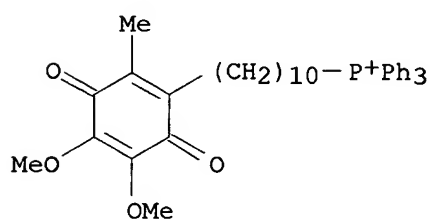
RN 845959-59-3 CAPLUS

CN  $\beta$ -Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium (2:1) (9CI) (CA INDEX NAME)

CM 1

CRN 444890-41-9

CMF C37 H44 O4 P



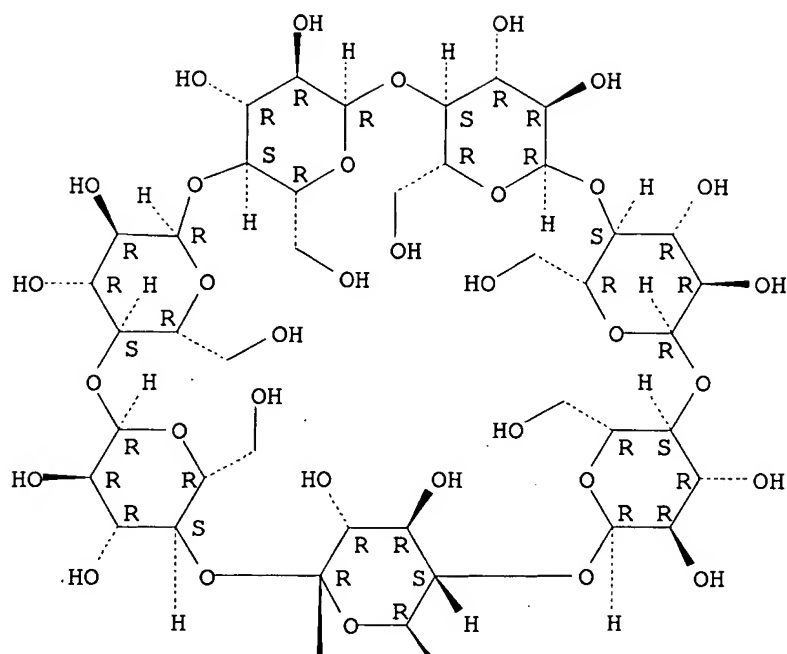
CM 2

CRN 7585-39-9

CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



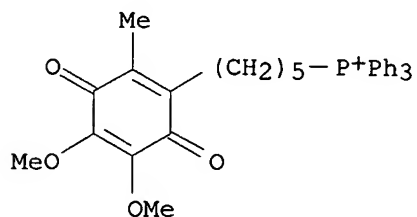
IT 764723-90-2P 764723-92-4P 845959-58-2P  
845959-60-6P

RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

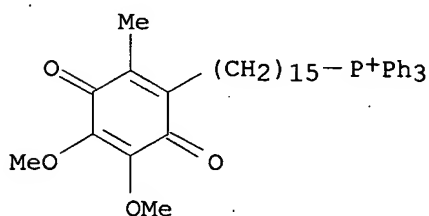
RN 764723-90-2 CAPLUS

CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)

● I<sup>-</sup>

RN 764723-92-4 CAPLUS

CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

● Br<sup>-</sup>

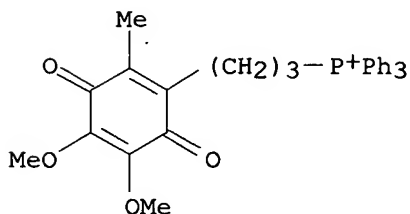
RN 845959-58-2 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 794485-93-1

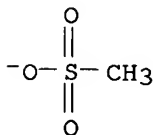
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CM 2

CRN 16053-58-0

CMF C H3 O3 S



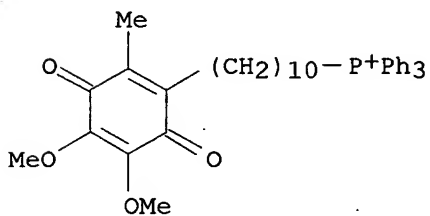
RN 845959-60-6 CAPLUS

CN  $\beta$ -Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium (4:1) (9CI) (CA INDEX NAME)

CM 1

CRN 444890-41-9

CMF C37 H44 O4 P



CM 2

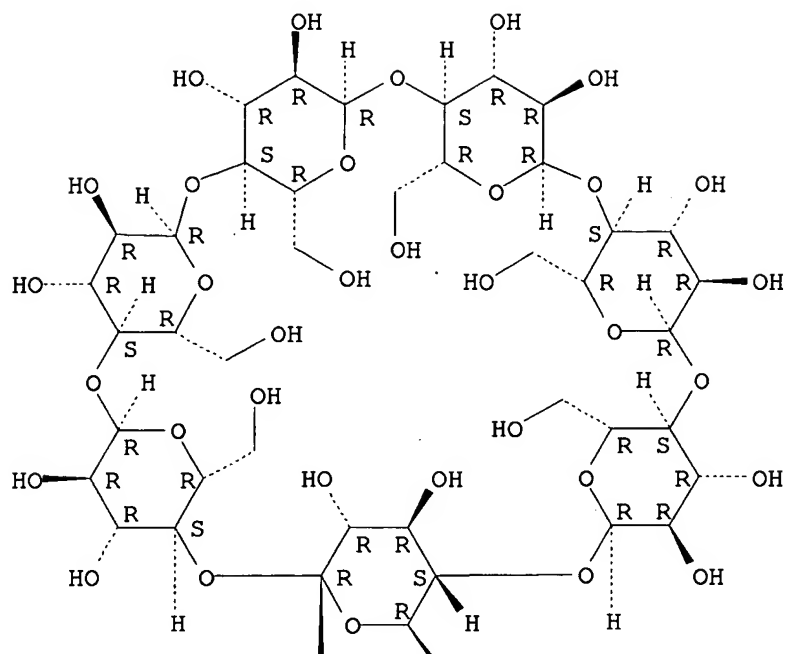
CRN 7585-39-9

CMF C42 H70 O35

Absolute stereochemistry.



PAGE 1-A



PAGE 2-A



IT 845959-56-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 845959-56-0 CAPLUS

CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (2:1) (9CI)  
(CA INDEX NAME)

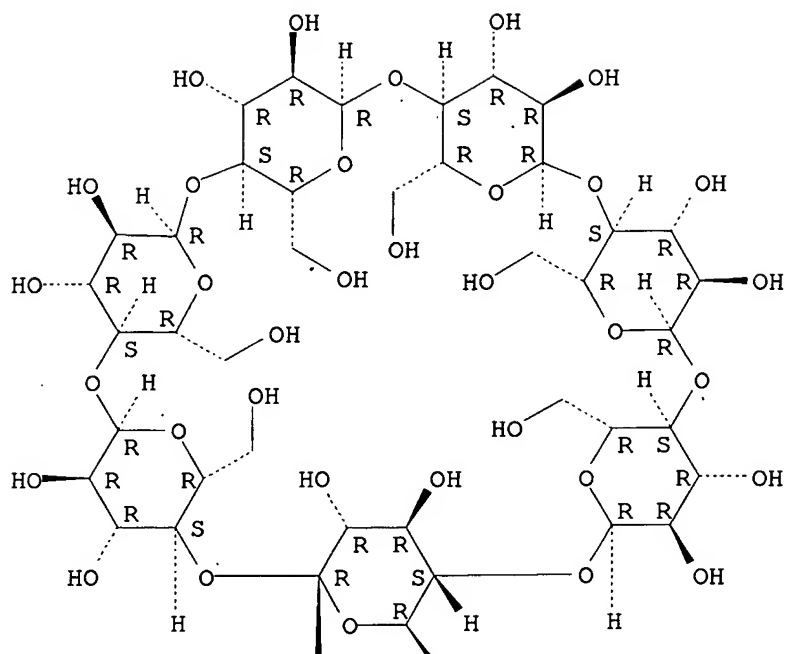
CM 1

CRN 7585-39-9

CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



CM 2

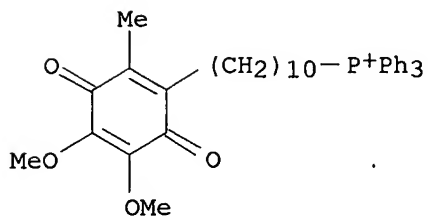
CRN 845959-50-4

CMF C37 H44 O4 P . C H3 O3 S

CM 3

CRN 444890-41-9

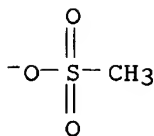
CMF C37 H44 O4 P



CM 4

CRN 16053-58-0

CMF C H3 O3 S

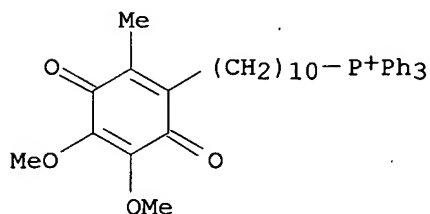


IT 444890-41-9 845959-51-5 845959-52-6

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)(mitoquinone derivative preparation for mitochondrially targeted  
antioxidant)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



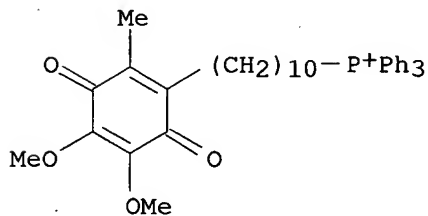
RN 845959-51-5 CAPLUS

CN  $\beta$ -Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 444890-41-9

CMF C37 H44 O4 P



CM 2

10/568,655

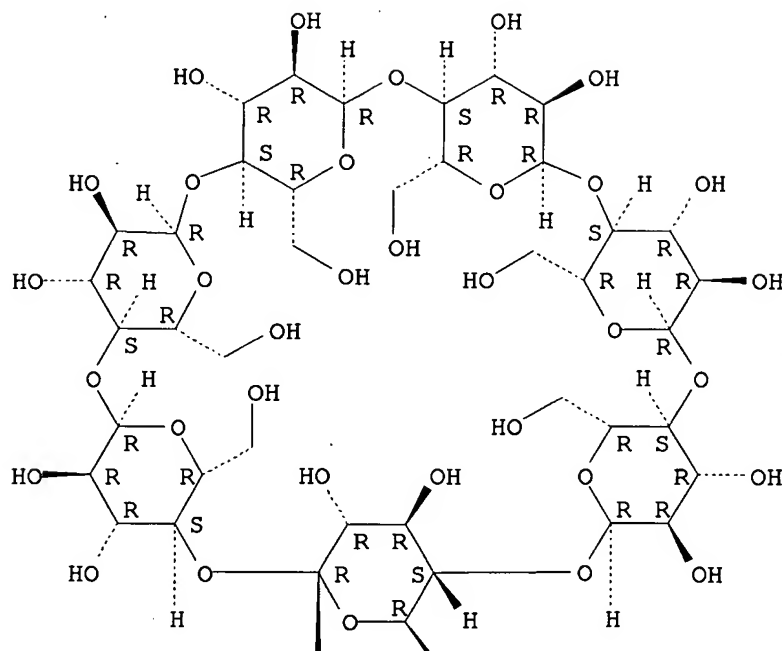
07/27/2008

CRN 7585-39-9

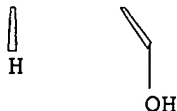
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



RN 845959-52-6 CAPLUS

CN  $\beta$ -Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (1:1) (9CI)  
(CA INDEX NAME)

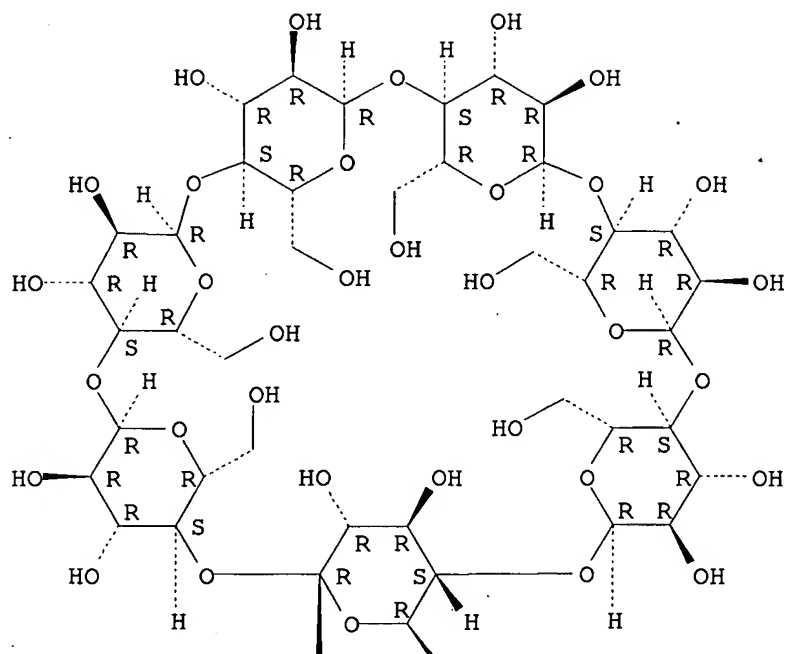
CM 1

CRN 7585-39-9

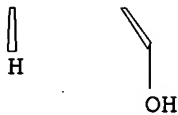
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



CM 2

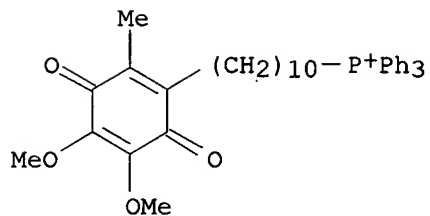
CRN 845959-50-4

CMF C37 H44 O4 P . C H3 O3 S

CM 3

CRN 444890-41-9

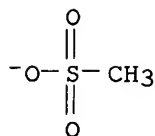
CMF C37 H44 O4 P



CM 4

CRN 16053-58-0

CMF C H3 O3 S



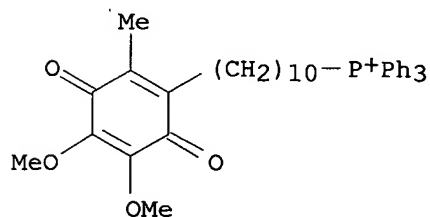
IT 336184-91-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 336184-91-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

● Br<sup>-</sup>

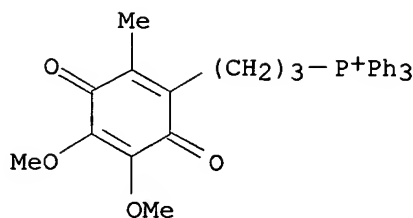
IT 845959-57-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 845959-57-1 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 28 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:710408 CAPLUS

DOCUMENT NUMBER: 141:236523

TITLE: Supplementation of Endothelial Cells with Mitochondria-targeted Antioxidants Inhibit Peroxide-induced Mitochondrial Iron Uptake, Oxidative Damage, and Apoptosis

AUTHOR(S): Dhanasekaran, Anuradha; Kotamraju, Srigiridhar; Kalivendi, Shasi V.; Matsunaga, Toshiyuki; Shang, Tiesong; Keszler, Agnes; Joseph, Joy; Kalyanaraman, B.  
CORPORATE SOURCE: Department of Biophysics and Free Radical Research Center, Medical College of Wisconsin, Milwaukee, WI, 53226, USA

SOURCE: Journal of Biological Chemistry (2004), 279(36), 37575-37587

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mitochondria-targeted drugs mitoquinone (Mito-Q) and mitovitamin E (MitoVit-E) are a new class of antioxidants containing the triphenylphosphonium cation moiety that facilitates drug accumulation in mitochondria. In this study, Mito-Q (ubiquinone attached to a triphenylphosphonium cation) and MitoVit-E (vitamin E attached to a triphenylphosphonium cation) were used. The aim of this study was to test the hypothesis that mitochondria-targeted antioxidants inhibit peroxide-induced oxidative stress and apoptosis in bovine aortic endothelial cells (BAEC) through enhanced scavenging of mitochondrial reactive oxygen species, thereby blocking reactive oxygen species-induced transferrin receptor (TfR)-mediated iron uptake into mitochondria. Glucose/glucose oxidase-induced oxidative stress in BAECs was monitored by oxidation of dichlorodihydrofluorescein that was catalyzed by both intracellular H<sub>2</sub>O<sub>2</sub> and transferrin iron transported into cells. Pretreatment of BAECs with Mito-Q (1 μM) and MitoVit-E (1 μM) but not untargeted antioxidants (e.g. vitamin E) significantly abrogated H<sub>2</sub>O<sub>2</sub>- and lipid peroxide-induced 2',7'-dichlorofluorescein fluorescence and protein oxidation. Mitochondria-targeted antioxidants inhibit cytochrome c release, caspase-3 activation, and DNA fragmentation. Mito-Q and MitoVit-E inhibited H<sub>2</sub>O<sub>2</sub>- and lipid peroxide-induced inactivation of

complex I and aconitase, TfR overexpression, and mitochondrial uptake of  $^{55}\text{Fe}$ , while restoring the mitochondrial membrane potential and proteasomal activity. The authors conclude that Mito-Q or MitoVit-E supplementation of endothelial cells mitigates peroxide-mediated oxidant stress and maintains proteasomal function, resulting in the overall inhibition of TfR-dependent iron uptake and apoptosis.

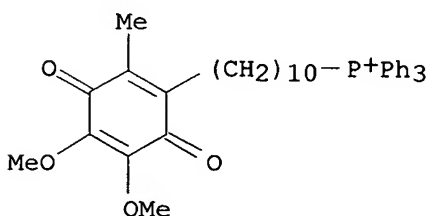
IT 336184-91-9

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(supplementation of endothelial cells with mitochondria-targeted antioxidants inhibit peroxide-induced mitochondrial iron uptake, oxidative damage, and apoptosis)

RN 336184-91-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 29 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:601038 CAPLUS

DOCUMENT NUMBER: 141:290668

TITLE: Fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant

AUTHOR(S): Asin-Cayuela, Jordi; Manas, Abdul-Rahman B.; James, Andrew M.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Wellcome Trust/MRC Building, Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK

SOURCE: FEBS Letters (2004), 571(1-3), 9-16

CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 141:290668

AB The mitochondria-targeted antioxidant MitoQ comprises a ubiquinol moiety covalently attached through an aliphatic carbon chain to the lipophilic triphenylphosphonium cation. This cation drives the membrane potential-dependent accumulation of MitoQ into mitochondria, enabling the ubiquinol antioxidant to prevent mitochondrial oxidative damage far more effectively than untargeted antioxidants. We sought to fine-tune the hydrophobicity of MitoQ so as to control the extent of its membrane binding and penetration into the phospholipid bilayer, and thereby regulate its partitioning between the membrane and aqueous phases within



mitochondria and cells. To do this, MitoQ variants with 3, 5, 10 and 15 carbon aliphatic chains were synthesized. These mols. had a wide range of hydrophobicities with octan-1-ol/phosphate buffered saline partition coeffs. from 2.8 to 20,000. All MitoQ variants were accumulated into mitochondria driven by the membrane potential, but their binding to phospholipid bilayers varied from negligible for MitoQ3 to essentially total for MitoQ15. Despite the span of hydrophobicities, all MitoQ variants were effective antioxidants. Therefore, it is possible to fine-tune the degree of membrane association of MitoQ and other mitochondria targeted compds., without losing antioxidant efficacy. This indicates how the uptake and distribution of mitochondria-targeted compds. within mitochondria and cells can be controlled, thereby facilitating investigations of mitochondrial oxidative damage.

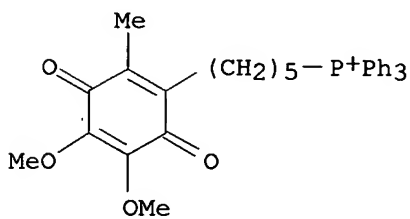
IT 764723-90-2P 764723-92-4P 845959-57-1P

RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation of MitoQ variants for fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant)

RN 764723-90-2 CAPLUS

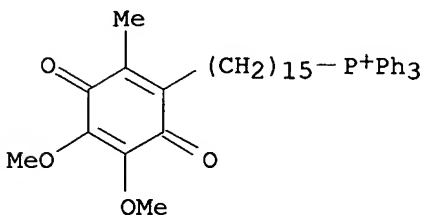
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



● I<sup>-</sup>

RN 764723-92-4 CAPLUS

CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

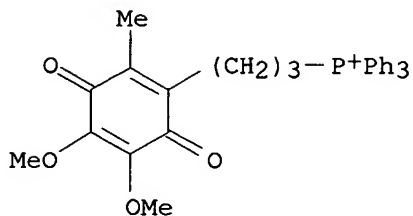


● Br<sup>-</sup>

RN 845959-57-1 CAPLUS

CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-

yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

IT 845959-58-2P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of MitoQ variants for fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant)

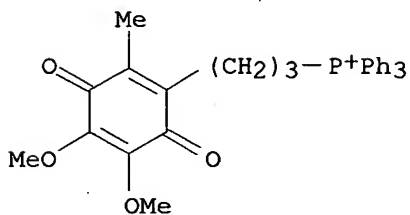
RN 845959-58-2 CAPLUS

CN Phosphonium, [3-((4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl)triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 794485-93-1

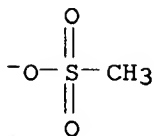
CMF C30 H30 O4 P



CM 2

CRN 16053-58-0

CMF C H3 O3 S



REFERENCE COUNT:

40

THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 30 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:434607 CAPLUS

DOCUMENT NUMBER: 141:49659

TITLE: Mitochondria-derived reactive oxygen species mediate blue light-induced death of retinal pigment epithelial cells

AUTHOR(S): King, Ayala; Gottlieb, Eyal; Brooks, David G.; Murphy, Michael P.; Dunaief, Joshua L.

CORPORATE SOURCE: F.M. Kirby Center for Molecular Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA, USA

SOURCE: Photochemistry and Photobiology (2004), 79(5), 470-475  
CODEN: PHCBAP; ISSN: 0031-8655

PUBLISHER: American Society for Photobiology

DOCUMENT TYPE: Journal

LANGUAGE: English

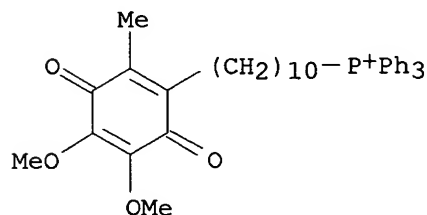
AB Throughout the lifetime of an individual, light is focused onto the retina. The resulting photooxidative stress can cause acute or chronic retinal damage. The pathogenesis of age-related macular degeneration (AMD), the leading cause of legal blindness in the developed world, involves oxidative stress and death of the retinal pigment epithelium (RPE) followed by death of the overlying photoreceptors. Evidence suggests that damage due to exposure to light plays a role in AMD and other age-related eye diseases. In this work a system for light-induced damage and death of the RPE, based on the human ARPE-19 cell line, was used. Induction of mitochondria-derived reactive oxygen species (ROS) is shown to play a critical role in the death of cells exposed to short-wavelength blue light ( $425 \pm 20$  nm). ROS and cell death are blocked either by inhibiting the mitochondrial electron transport chain or by mitochondria-specific antioxidants. These results show that mitochondria are an important source of toxic oxygen radicals in blue light-exposed RPE cells and may indicate new approaches for treating AMD using mitochondria-targeted antioxidants.

IT 336184-91-9

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(mitochondria-derived ROS mediate blue light-induced death of retinal pigment epithelium)

RN 336184-91-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

● Br<sup>-</sup>

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 31 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:826167 CAPLUS

DOCUMENT NUMBER: 140:53354

TITLE: Mitochondria-targeted antioxidants protect Friedreich Ataxia fibroblasts from endogenous oxidative stress more effectively than untargeted antioxidants

AUTHOR(S): Jauslin, Matthias L.; Meier, Thomas; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: MyoContract Ltd., Liestal, CH-4410, Switz.

SOURCE: FASEB Journal (2003), 17(13), 1972-1974, 10.1096/fj.03-0240fje

CODEN: FAJOEC; ISSN: 0892-6638

PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Friedreich Ataxia (FRDA), the most common inherited ataxia, arises from defective expression of the mitochondrial protein frataxin, which leads to increased mitochondrial oxidative damage. Therefore, antioxidants targeted to mitochondria should be particularly effective at slowing disease progression. To test this hypothesis, we compared the efficacy of mitochondria-targeted and untargeted antioxidants derived from coenzyme Q10 and from vitamin E at preventing cell death due to endogenous oxidative stress in cultured fibroblasts from FRDA patients in which glutathione synthesis was blocked. The mitochondria-targeted antioxidant MitoQ was several hundredfold more potent than the untargeted analog idebenone. The mitochondria-targeted antioxidant MitoVit E was 350-fold more potent than the water soluble analog Trolox. This is the first demonstration that mitochondria-targeted antioxidants prevent cell death that arises in response to endogenous oxidative damage. Targeted antioxidants may have therapeutic potential in FRDA and in other disorders involving mitochondrial oxidative damage.

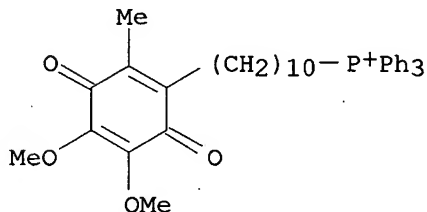
IT 444890-41-9

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mitochondria-targeted antioxidants protect Friedreich Ataxia fibroblasts from endogenous oxidative stress more effectively than untargeted antioxidants)

RN 444890-41-9 CAPLUS

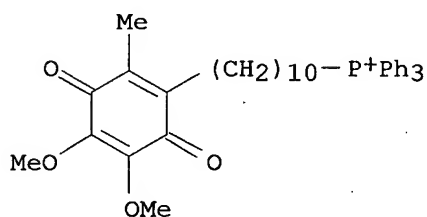
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 32 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:426934 CAPLUS  
DOCUMENT NUMBER: 140:74526  
TITLE: MitoQ counteracts telomere shortening and elongates lifespan of fibroblasts under mild oxidative stress  
AUTHOR(S): Saretzki, Gabriele; Murphy, Michael P.; von Zglinicki, Thomas  
CORPORATE SOURCE: Gerontology, Institute of Aging and Health, Newcastle University, Newcastle upon Tyne, NE4 6BE, UK  
SOURCE: Aging Cell (2003), 2(2), 141-143  
CODEN: ACGECQ; ISSN: 1474-9718  
PUBLISHER: Blackwell Publishing Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB The effect of the mitochondria-specific antioxidant mitoQ [10-(6'-ubiquinonyl) decyltriphenylphosphonium bromide] in human fibroblasts under mild stress conditions was investigated. Treatment of MRC-5 fibroblasts with mitoQ under these conditions significantly decreased the cellular peroxide content and elongated the replicative lifespan. MitoQ treatment completely prevented the rise in telomere shortening rate due to hyperoxia and instead gave a negligible rate of telomere shortening.  
IT 336184-91-9  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (MitoQ counteracts telomere shortening and elongates lifespan of human fibroblasts under mild oxidative stress)  
RN 336184-91-9 CAPLUS  
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

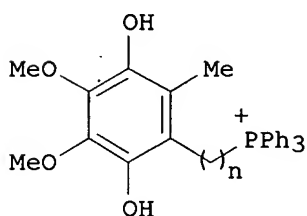
L3 ANSWER 33 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:154438 CAPLUS  
DOCUMENT NUMBER: 138:187926  
TITLE: Preparation of triphenylphosphonium quinols and quinones  
INVENTOR(S): Smith, Robin; Murphy, Michael Patrick  
PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.  
SOURCE: PCT Int. Appl., 13 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English

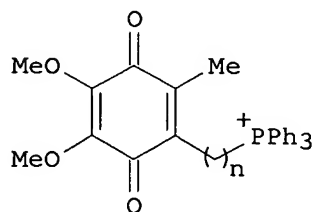
FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003016323	A1	20030227	WO 2002-NZ154	20020812
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
NZ 513547	A	20020927	NZ 2001-513547	20010813
AU 2002326242	A1	20030303	AU 2002-326242	20020812
EP 1423396	A1	20040602	EP 2002-760924	20020812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 20050043553	A1	20050224	US 2004-486797	20041001
US 7179928	B2	20070220		
PRIORITY APPLN. INFO.:			NZ 2001-513547	A 20010813
			WO 2002-NZ154	W 20020812
OTHER SOURCE(S):			CASREACT 138:187926; MARPAT 138:187926	
GI				



I



II

AB Triphenylphosphonium quinols and quinones [e.g., I and II, resp.; wherein n = integer from 6 to 40] were prepared. For example, Idebenone is reacted with PPh<sub>3</sub> and PPh<sub>3</sub>•HBr to give 57% MitoQuinol I Br<sup>-</sup> (n = 10), which is purified and oxidized with H<sub>2</sub>O<sub>2</sub>/pyridine to give 77% MitoQuinone II Br<sup>-</sup> (n = 10).

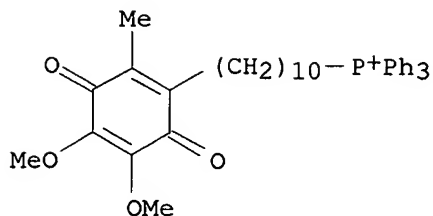
IT 336184-91-9P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of triphenylphosphonium quinols and quinones)

RN 336184-91-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 34 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:411988 CAPLUS

DOCUMENT NUMBER: 137:139797

TITLE: Prevention of mitochondrial oxidative damage using targeted antioxidants

AUTHOR(S): Kelso, Geoffrey F.; Porteous, Carolyn M.; Hughes, Gillian; Ledgerwood, Elizabeth C.; Gane, Alison M.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Departments of Chemistry, University of Otago, Dunedin, N. Z.

SOURCE: Annals of the New York Academy of Sciences (2002), 959(Increasing Health Life Span), 263-274

CODEN: ANYAA9; ISSN: 0077-8923

PUBLISHER: New York Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two mitochondria-targeted antioxidants that can selectively block mitochondrial oxidative damage and prevent some types of cell death were developed. They were ubiquinone and tocopherol derivs. targeted to mitochondria by covalent attachment to the lipophilic triphenylphosphonium cation. The effects of the 2 derivs. and nontargeted ubiquinone and tocopherol were examined in vitro in rat liver and beef heart mitochondrial preps. and in Jurkat human T lymphocyte cell line and in vivo in female Swiss Webster mice. Because of the large mitochondrial membrane potential, these cations can accumulated within mitochondria inside the cells, where the antioxidant moiety prevented lipid peroxidn. and protected the mitochondria from oxidative damage. The mitochondrially localized ubiquinone derivative also protected mammalian cells from hydrogen peroxide-induced apoptosis while the nontargeted ubiquinone analog was ineffective against cell apoptosis. When fed to mice, the 2 derivs. accumulated in the brain, heart, and liver. These mitochondria-targeted antioxidants may help in investigations of the role of mitochondrial oxidative damage in animal models of aging.

IT 444890-41-9

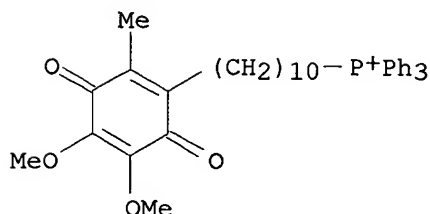
RL: BSU (Biological study, unclassified); FFD (Food or feed use); BIOL (Biological study); USES (Uses)

(dietary ubiquinone and tocopherol targeted antioxidant derivs. use in prevention of mitochondrial oxidative damage in vitro and in mice)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-

yl)decyl]triphenyl- (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 35 OF 35 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:137933 CAPLUS

DOCUMENT NUMBER: 134:322127

TITLE: Selective targeting of a redox-active ubiquinone to mitochondria within cells. Antioxidant and antiapoptotic properties

AUTHOR(S): Kelso, Geoffrey F.; Porteous, Carolyn M.; Coulter, Carolyn V.; Hughes, Gillian; Porteous, William K.; Ledgerwood, Elizabeth C.; Smith, Robin A. J.; Murphy, Michael P.

CORPORATE SOURCE: Department of Chemistry, University of Otago, Dunedin, N. Z.

SOURCE: Journal of Biological Chemistry (2001), 276(7), 4588-4596

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 134:322127

AB With the recognition of the central role of mitochondria in apoptosis, there is a need to develop specific tools to manipulate mitochondrial function within cells. Here we report on the development of a novel antioxidant that selectively blocks mitochondrial oxidative damage, enabling the roles of mitochondrial oxidative stress in different types of cell death to be inferred. This antioxidant, named mitoQ, is a ubiquinone derivative targeted to mitochondria by covalent attachment to a lipophilic triphenylphosphonium cation through an aliphatic carbon chain. Due to the large mitochondrial membrane potential, the cation was accumulated within mitochondria inside cells, where the ubiquinone moiety inserted into the lipid bilayer and was reduced by the respiratory chain. The ubiquinol derivative thus formed was an effective antioxidant that prevented lipid peroxidn. and protected mitochondria from oxidative damage. After detoxifying the reactive oxygen species peroxynitrite, the ubiquinol moiety was regenerated by the respiratory chain enabling its antioxidant activity to be recycled. In cell culture studies, the mitochondrially localized antioxidant protected mammalian cells from hydrogen peroxide-induced apoptosis but not from apoptosis induced by staurosporine or tumor necrosis factor- $\alpha$ . This was compared with untargeted ubiquinone analogs, which were ineffective in preventing apoptosis. These results suggest that mitochondrial oxidative stress may be a critical step in apoptosis induced by hydrogen peroxide but not for apoptosis induced by



staurosporine or tumor necrosis factor- $\alpha$ . We have shown that selectively manipulating mitochondrial antioxidant status with targeted and recyclable antioxidants is a feasible approach to investigate the role of mitochondrial oxidative damage in apoptotic cell death. This approach will have further applications in investigating mitochondrial dysfunction in a range of exptl. models.

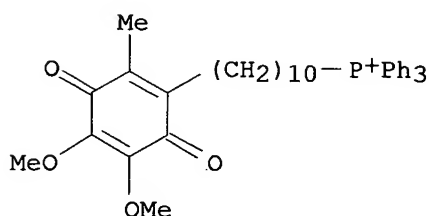
IT 336184-91-9P 336184-92-0P

RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)

(novel redox-active ubiquinone mitoQ displays antioxidant and antiapoptotic properties in mitochondria)

RN 336184-91-9 CAPLUS

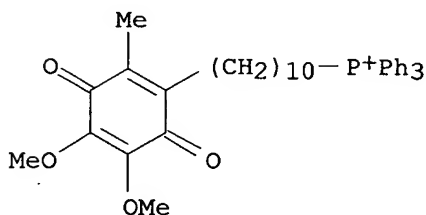
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● Br<sup>-</sup>

RN 336184-92-0 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide, labeled with tritium (9CI) (CA INDEX NAME)



● Br<sup>-</sup>

REFERENCE COUNT:

49

THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

---Logging off of STN---

10/568,655

07/27/2008

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Executing the logoff script...

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COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

191.71

370.28

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

-28.00

-28.00

STN INTERNATIONAL LOGOFF AT 17:09:44 ON 27 JUL 2008